

PRODUCT MONOGRAPH

CERVARIX™

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

Suspension for injection

Active immunizing agent

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Date of Revision:
February 05, 2010

Submission Control No:

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CERVARIX™

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

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength per 0.5 mL dose	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection	Suspension for injection/ 20 µg Human Papillomavirus (HPV) type 16 L1 protein, 20 µg Human Papillomavirus (HPV) type 18 L1 protein	3- <i>O</i> -desacyl-4'-monophosphoryl lipid A (MPL), aluminum hydroxide, hydrated sodium chloride, sodium dihydrogen phosphate dihydrate, water for injection

DESCRIPTION

CERVARIX™ (Human Papillomavirus vaccine Types 16 and 18 [Recombinant, AS04 adjuvanted]) is a non-infectious recombinant, AS04-adjuvanted vaccine.

This vaccine contains recombinant C-terminally truncated L1 proteins from 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. The adjuvant system, AS04, is composed of 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL) adsorbed onto aluminum (as hydroxide salt).

INDICATIONS AND CLINICAL USE

CERVARIX™ is a vaccine indicated in females from 10 to 25 years of age for the prevention of cervical cancer (squamous cell cancer and adenocarcinoma) by protecting against the following precancerous or dysplastic lesions caused by oncogenic Human Papillomavirus (HPV), types 16 and 18:

- Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1

Pediatrics: See Part II, CLINICAL TRIALS.

CONTRAINDICATIONS

CERVARIX™ should not be administered in:

- females with a known hypersensitivity to any component in the vaccine. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

General

CERVARIX™ is a prophylactic vaccine. It does not prevent progression of HPV-related lesions present at the time of vaccination.

CERVARIX™ does not provide protection against all oncogenic HPV types and may not prevent infection with HPV-16/18 or subsequent progression to Cervical Carcinoma, in all vaccine recipients.

CERVARIX™ is not a treatment for current HPV infection, precancerous lesions, or cervical cancer.

It is good clinical practice that the vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination if indicated.

Vaccination is for primary prevention and is not a substitute for regular cervical screening (secondary prevention) or for precautions against exposure to HPV and other sexually transmitted diseases. All women should continue to follow recommended cervical cancer screening procedures.

Prior to administration, the healthcare provider should review the immunization history for possible vaccine hypersensitivity and previous vaccination-related adverse reactions

to allow an assessment of benefits and risks. As with any injectable vaccine, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Precautions should be taken to avoid intravascular administration.

Febrile Illness

As with other vaccines, administration of CERVARIX™ should be postponed in individuals 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.

Hematologic

As with all 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 individuals.

Immune

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

There are no data on the use of CERVARIX™ in individuals with impaired immune responsiveness such as HIV infected patients or patients receiving immunosuppressive treatment. For those individuals an adequate immune response may not be elicited. The duration of protection has not been established (see CLINICAL TRIALS).

Syncope

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with CERVARIX™. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

Special Populations

Pregnant Women:

Vaccination should not be undertaken in women who are pregnant and vaccinees should be advised to take adequate precautions to avoid pregnancy for 2 months following vaccination (see CLINICAL TRIALS, Pregnancy Outcomes).

Patients and healthcare providers are encouraged to report any exposure to CERVARIX™ vaccine during Pregnancy by calling 1-800-387-7374.

Spontaneous Abortions:

Outcomes Around Time of Vaccination: In 761 women who had their last menstrual period within 30 days prior to, or 45 days after a vaccine dose and for whom pregnancy outcome was known, spontaneous abortion occurred in a higher proportion of women who received CERVARIX™ (13.6%) compared to those receiving a control substance (9.6%). It is not known if this is due to a vaccine related effect (see CLINICAL TRIALS, Pregnancy Outcomes).

Nursing Women:

The effect on breastfed infants of the administration of CERVARIX™ to their mothers has not been evaluated in clinical studies. CERVARIX™ should only be used during breast-feeding when the possible advantages outweigh the possible risks.

Serological data suggest a transfer of anti-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.

Pediatrics:

CERVARIX™ is not indicated for children younger than 10 years of age (see ADVERSE REACTIONS and CLINICAL STUDIES). Safety and effectiveness in pediatric patients younger than 10 years of age have not been established.

ADVERSE REACTIONS**Clinical Trial Adverse Drug Reactions**

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reactions information from clinical trials is useful for identifying drug-related adverse events for approximating rates.

Studies in Females 10 Through 25 Years of Age: The safety of CERVARIX™ was evaluated by pooling data from controlled and uncontrolled clinical trials involving 23,713 females 10 through 25 years of age in the pre-licensure clinical development program. In these studies, 12,785 females (10 through 25 years of age [of these; 1193 of the female children were 10 through 14 years of age and 6316 were 15 through 17 years of age]) received at least one dose of CERVARIX™ and 10,298 females received at least one dose of a control [Hepatitis A Vaccine containing 360 EL.U. (10 through 14 years of age), Hepatitis A Vaccine containing 720 EL.U. (15 through 25 years of age), or Al(OH)₃ (500 µg, 15 through 25 years of age)].

Compliance with the full vaccination course was equally high in both the HPV vaccine and control groups.

Data on solicited local and general adverse events were collected by subjects or parents using standardized diary cards for 7 consecutive days following each vaccine dose (i.e., day of vaccination and the next 6 days). Unsolicited adverse events were recorded with diary cards for 30 days following each vaccination (day of vaccination and 29 subsequent days). Parents and/or subjects were also asked at each study visit about the occurrence of any adverse events and instructed to immediately report serious adverse events throughout the study period. These studies were conducted in North America, Latin America, Europe, Asia, and Australia.

Solicited Adverse Events

The reported frequencies of solicited local injection site reactions (pain, redness, and swelling) and general adverse events (fatigue, fever, gastrointestinal symptoms, headache, arthralgia, myalgia, and urticaria) within 7 days after vaccination in females 10 through 25 years of age are presented in Table 1. An analysis of solicited local injection site reactions by dose is presented in Table 2. Local reactions were reported more frequently with CERVARIX™ when compared with the control groups; in $\geq 84\%$ of recipients of CERVARIX™, these local reactions were mild to moderate in intensity. Compared with dose 1, pain was reported less frequently after doses 2 and 3 of CERVARIX™, in contrast to redness and swelling where there was a small increased incidence. There was no increase in the frequency of general adverse events with successive doses.

Table 1 Rates of Solicited Local Adverse Reactions and General Adverse Events in Females 10 Through 25 Years of Age Within 7 Days of Vaccination (Total Vaccinated Cohort^a)

Adverse Reaction/Event	CERVARIX™ [*] (10-25 yrs) %	HAV 720 ^b (15-25 yrs) %	HAV 360 ^c (10-14 yrs) %	Al(OH) ₃ Control ^d (15-25 yrs) %
Local Adverse Reaction	N=6431	N=3079	N=1027	N=549
Pain	91.8	78.0	64.2	87.2
Redness	48.0	27.6	25.2	24.4
Swelling	44.1	19.8	17.3	21.3
General Adverse Event	N=6432	N=3079	N=1027	N=549
Fatigue	55.0	53.7	42.3	53.6
Headache	53.4	51.3	45.2	61.4
GI ^e	27.8	27.3	24.6	32.8
Fever (≥99.5°F)	12.8	10.9	16.0	13.5
Rash	9.6	8.4	6.7	10.0
	N=5881	N=3079	N=1027	-
Myalgia ^f	49.1	44.9	33.1	-
Arthralgia ^f	20.8	17.9	19.9	-
Urticaria ^f	7.4	7.9	5.4	-

^aTotal vaccinated cohort included subjects with at least one documented dose (N).

^bHAV 720 = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 µg Al(OH)₃].

^cHAV 360 = Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 µg of Al(OH)₃].

^dAl(OH)₃ Control = control containing 500 µg Al(OH)₃.

^eGI = Gastrointestinal symptoms, including nausea, vomiting, diarrhea, and/or abdominal pain.

^fAdverse events solicited in a subset of subjects.

* The number of subjects in the CERVARIX™ group for Local Adverse Reactions and General Adverse Events varies (6431 and 6432 respectively). The number of subjects included in the analysis is the number of subjects with a documented dose (for Local Adverse Reactions, there was one less subject with a documented dose).

Studies: HPV-001, 008 diary card subset, 012, 013, 014, 016.

Table 2 Rates of Solicited Local Adverse Reactions in Females 10 Through 25 Years of Age by Dose Within 7 Days of Vaccination (Total Vaccinated Cohort^a)

Adverse Reaction	CERVARIX™ (10-25 yrs) %			HAV 720 ^b (15-25 yrs) %			HAV 360 ^c (10-14 yrs) %			Al(OH) ₃ Control ^d (15-25 yrs) %		
	Post-Dose			Post-Dose			Post-Dose			Post-Dose		
	1	2	3	1	2	3	1	2	3	1	2	3
N	6415	6197	5936	3070	2919	2758	1027	1021	1011	546	521	500
Pain	86.9	76.2	78.7	65.6	54.4	56.1	48.5	38.5	36.9	79.1	66.8	72.4
Pain, Grade 3 ^e	7.5	5.7	7.7	2.0	1.4	2.0	0.8	0.2	1.6	9.0	6.0	8.6
Redness	27.8	29.6	35.6	16.6	15.2	16.1	15.6	13.3	12.1	11.5	11.5	15.6
Redness, >50 mm	0.2	0.5	1.0	0.1	0.1	0.0	0.1	0.2	0.1	0.2	0.0	0.0
Swelling	22.7	25.2	32.7	10.5	9.4	10.5	9.4	8.6	7.6	10.3	10.4	12.0
Swelling, >50 mm	1.2	1.0	1.3	0.2	0.2	0.2	0.4	0.3	0.0	0.0	0.0	0.0

^a Total vaccinated cohort included subjects with at least one documented dose (N).

^b HAV 720 = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 µg Al(OH)₃].

^c HAV 360 = Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 µg of Al(OH)₃].

^d Al(OH)₃ Control = control containing 500 µg Al(OH)₃.

^e Defined as spontaneously painful or pain that prevented normal daily activities.

The pattern of solicited local adverse reactions and general adverse events following administration of CERVARIX™ was similar between the age cohorts (10 through 14 years and 15 through 25 years).

Unsolicited Adverse Events by Subject

The frequency of unsolicited adverse events that occurred within 30 days of vaccination (≥1% for CERVARIX™ and greater than any of the control groups) in females 10 through 25 years of age are presented in Table 3.

Table 3 Rates of Unsolicited Adverse Events in Females 10 Through 25 Years of Age Within 30 Days of Vaccination ($\geq 1\%$ For CERVARIX™ and Greater Than HAV 720, HAV 360, or Al(OH)₃ Control) (Total Vaccinated Cohort^a)

Adverse Event	CERVARIX™ [*] % N=6654	HAV 720 ^b % N=3186	HAV 360 ^c % N=1032	Al(OH) ₃ Control ^d % N=581
Headache	5.3	7.6	3.3	9.3
Nasopharyngitis	3.6	3.4	5.9	3.3
Influenza	3.2	5.6	1.3	1.9
Pharyngolaryngeal pain	2.9	2.7	2.2	2.2
Dizziness	2.2	2.6	1.5	3.1
Upper respiratory tract infection	2.0	1.3	6.7	1.5
Chlamydia infection	2.0	4.4	0.0	0.0
Dysmenorrhea	2.0	2.3	1.9	4.0
Pharyngitis	1.5	1.8	2.2	0.5
Injection site bruising	1.4	1.8	0.7	1.5
Vaginal infection	1.4	2.2	0.1	0.9
Injection site pruritus	1.3	0.5	0.6	0.2
Back pain	1.1	1.3	0.7	3.1
Urinary tract infection	1.0	1.4	0.3	1.2

^a Total vaccinated cohort included subjects with at least one documented dose (N).

^b HAV 720 = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 µg Al(OH)₃].

^c HAV 360 = Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 µg of Al(OH)₃].

^d Al(OH)₃ Control = control containing 500 µg Al(OH)₃.

* The number of subjects in the CERVARIX™ group varies between Table 1 and Table 3 because Table 3 included subjects from studies HPV-001, 003, 004, 005, 008 diary card subset, 012, 013, 014, 016.

Serious Adverse Events (SAEs)

In the pooled safety database, inclusive of controlled and uncontrolled studies, which enrolled females 10 through 72 years of age, 5.3% (862/16,142) of subjects who received CERVARIX™ and 5.9% (814/13,811) of subjects who received control reported at least one serious adverse event, without regard to causality, during the entire follow-up period (up to 7.4 years). Among females 10 through 25 years of age enrolled in these clinical studies, 6.4% of subjects who received CERVARIX™ and 7.2% of subjects who received the control reported at least one serious adverse event during the entire follow-up period (up to 7.4 years).

Deaths

In completed and ongoing studies which enrolled 57,323 females 9 through 72 years of age, 37 deaths were reported during the 7.4 years of follow-up: 20 in subjects who received CERVARIX™ (0.06%, 20/33,623) and 17 in subjects who received control (0.07%, 17/23,700). Causes of death among subjects were consistent with those reported in adolescent and adult female populations. The most common causes of death were motor vehicle accident (5 subjects who received CERVARIX™; 5 subjects who received

control) and suicide (2 subjects who received CERVARIX™; 5 subjects who received control), followed by neoplasm (3 subjects who received CERVARIX™; 2 subjects who received control), autoimmune disease (3 subjects who received CERVARIX™; 1 subject who received control), infectious disease (3 subjects who received CERVARIX™; 1 subject who received control), homicide (2 subjects who received CERVARIX™; 1 subject who received control), cardiovascular disorders (2 subjects who received CERVARIX™), and death of unknown cause (2 subjects who received control). Among females 10 through 25 years of age, 31 deaths were reported (0.05%, 16/29,467 of subjects who received CERVARIX™ and 0.07%, 15/20,192 of subjects who received control).

New Onset Autoimmune Diseases (NOADs)

The pooled safety database, which included controlled and uncontrolled trials which enrolled females 10 through 25 years of age, was searched for new medical conditions indicative of potential new onset autoimmune diseases. Overall, the incidence of potential NOADs, as well as NOADs in the group receiving CERVARIX™ was 0.8% (95/12,533) and comparable to the pooled control group (0.8%, 87/10,730) during the 4.3 years of follow-up (mean 3.0 years) (Table 4). In the largest randomized, controlled trial (Study HPV-008) which enrolled females 15 through 25 years of age and which included active surveillance for potential NOADs, the incidence of potential NOADs and NOADs was 0.8% among subjects who received CERVARIX™ (78/9319) and 0.8% among subjects who received Hepatitis A Vaccine [720 EL.U. of antigen and 500 µg Al(OH)₃] control (77/9235).

Table 4 Incidence of New Medical Conditions Indicative of Potential New Onset Autoimmune Disease and New Onset Autoimmune Disease Throughout the Follow-up Period Regardless of Causality in Females 10 Through 25 Years of Age (Total Vaccinated Cohort^a)

	CERVARIX™ (N=12,533)	Pooled Control Group^b (N=10,730)
	n (%)^c	n (%)^c
Total Number of Subjects With at Least One Medical Condition	95 (0.8)	87 (0.8)
Arthritis ^d	9 (0.0)	4 (0.0)
Celiac disease	2 (0.0)	5 (0.0)
Dermatomyositis	0 (0.0)	1 (0.0)
Diabetes mellitus insulin-dependent (Type 1 or unspecified)	5 (0.0)	5 (0.0)
Erythema nodosum	3 (0.0)	0 (0.0)
Hyperthyroidism ^e	14 (0.1)	15 (0.1)
Hypothyroidism ^f	30 (0.2)	28 (0.3)
Inflammatory bowel disease ^g	8 (0.1)	4 (0.0)
Multiple sclerosis	4 (0.0)	1 (0.0)
Myelitis transverse	1 (0.0)	0 (0.0)
Optic neuritis/Optic neuritis retrobulbar	3 (0.0)	1 (0.0)
Psoriasis ^h	8 (0.1)	11 (0.1)
Raynaud's phenomenon	0 (0.0)	1 (0.0)
Rheumatoid arthritis	4 (0.0)	3 (0.0)
Systemic lupus erythematosus ⁱ	2 (0.0)	3 (0.0)
Thrombocytopenia ^j	1 (0.0)	1 (0.0)
Vasculitis ^k	1 (0.0)	3 (0.0)
Vitiligo	2 (0.0)	2 (0.0)

^a Total vaccinated cohort included subjects with at least one documented dose (N).

^b Pooled Control Group = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 µg Al(OH)₃], Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 µg of Al(OH)₃], and a control containing 500 µg Al(OH)₃.

^c n (%): number and percentage of subjects with medical condition.

^d Term includes reactive arthritis and arthritis.

^e Term includes Basedow's disease, goiter, and hyperthyroidism.

^f Term includes thyroiditis, autoimmune thyroiditis, and hypothyroidism.

^g Term includes colitis ulcerative, Crohn's disease, proctitis ulcerative, and inflammatory bowel disease.

^h Term includes psoriatic arthropathy, nail psoriasis, guttate psoriasis, and psoriasis.

ⁱ Term includes systemic lupus erythematosus and cutaneous lupus erythematosus.

^j Term includes idiopathic thrombocytopenic purpura and thrombocytopenia.

^k Term includes leukocytoclastic vasculitis and vasculitis.

Post-Marketing Adverse Drug Reactions

The following events have been spontaneously reported during post-approval use of CERVARIX™. This list includes serious events or events which have suspected causal association to CERVARIX™. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccination.

Immune System Disorders

Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema and erythema multiforme have been rarely reported ($\geq 1/10,000$ to $< 1/1000$).

Nervous System Disorders

Syncope or vasovagal responses to injection (sometimes accompanied by tonic-clonic movements) have been rarely reported ($\geq 1/10,000$ to $< 1/1000$).

DRUG INTERACTIONS

Drug-Drug Interactions

Use with other vaccines

Studies to evaluate the concomitant administration of CERVARIX™ and other vaccines (conjugate meningococcal vaccine, Hepatitis B vaccine, Hepatitis A and B vaccine and adult/adolescent formulations of tetanus, diphtheria, acellular pertussis (dTpa)) are currently on-going.

Data have not been generated on the concomitant administration of CERVARIX™ and other vaccines. If CERVARIX™ is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites. CERVARIX™ should not be mixed with any other vaccine in the same syringe or vial.

Use with hormonal contraceptives

In clinical efficacy studies, approximately 60% of females 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 therapy, an adequate response may not be achieved.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Effects on the ability to drive and use machines

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

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

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 can be administered between 5 months and 9 months after the first dose. The necessity for a booster has not been established.

Administration

CERVARIX™ is for intramuscular injection in the deltoid region. Do not administer this product intradermally, or subcutaneously and precautions should be taken to avoid intravascular administration.

A fine white deposit with a clear, colourless supernatant may be observed upon storage of the syringe/vial. This does not constitute a sign of deterioration.

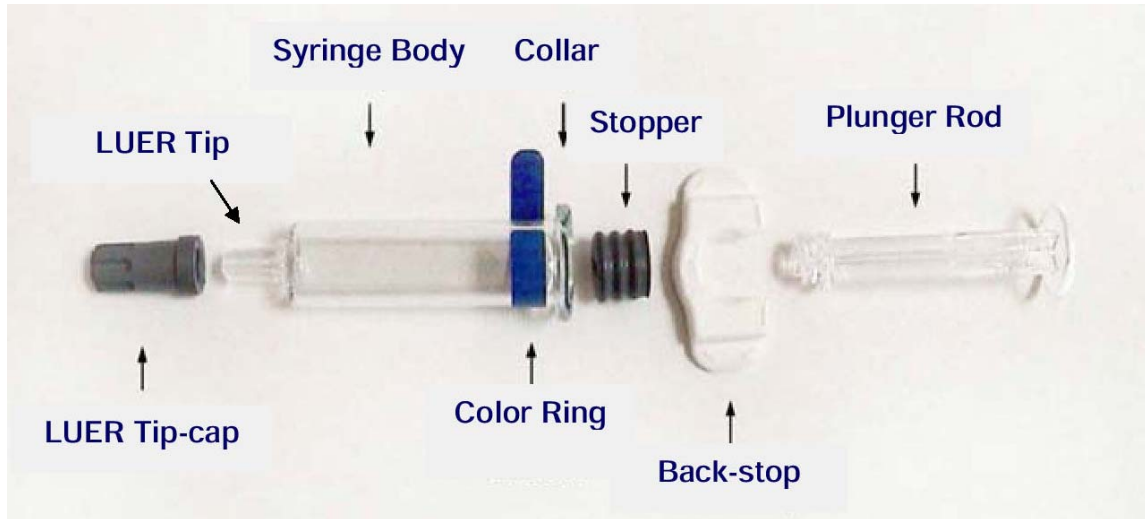
The content of the syringe/vial should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.

Shake well before use.

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

Preparation for Administration

The syringe comes fully assembled. **Do not remove the white back-stop from the syringe.** Prior to administration, ensure that the plunger rod is firmly attached to the rubber stopper by turning the plunger clockwise until slight resistance is felt. **Do not** over tighten. Holding the syringe barrel in one hand (avoid holding the syringe plunger), remove the syringe LUER Tip-cap and needle cap by twisting anticlockwise. Attach needle by pressing and twisting in a clockwise rotation until secured to the syringe. Remove the needle protector, which on occasion can be a little stiff. Administer the vaccine.



OVERDOSAGE

Insufficient data are available.

ACTION AND CLINICAL PHARMACOLOGY

Disease Burden

Worldwide, oncogenic Human Papillomavirus (HPV) types are the necessary cause of cervical cancer. Compelling epidemiological evidence confirms that persistent infection with oncogenic HPV types is responsible for virtually all cases of invasive cervical cancer. Based on a large consensus among experts, the most common HPV types identified in cervical cancer worldwide were, in decreasing order of frequency, HPV-16, -18, -45, -31, -33, -52, -58, -35, -59, -56, -39, -51, -73, -68 and -66. HPV types -16 and -18 are responsible for more than 70% of invasive cervical cancers. Together, HPV types -16, -18, -31 and -45 account for up to 80.3% of cases. In the United States, the most common HPV genotypes detected in invasive cancers are HPV type -16 (HPV-16, 53.2%), HPV-18 (13.1%), and HPV-45 (6.1%) and those in *in situ* cancers were HPV-16 (56.3%), HPV-31 (12.6%), and HPV-33 (8.0%). HPV is a highly prevalent family of viruses. Up to 80% of females who have ever been sexually active will acquire an HPV infection in their lifetime, which in some cases may cause cervical cancer. Oncogenic HPV types have been found in up to 75% of HPV infections.

Cervical cancers begin as asymptomatic precancerous lesions and usually develop gradually over many years. Cervical lesions are described according to the degree of cytopathology found on the Pap¹ smear, with progression in degree of dysplasia.

¹ Pap (Papanicolaou test detects abnormal cervical cells)

HPV is generally transmitted via skin-to-skin contact during sexual activity. Papillomavirus entry into cells may take as little as 2 to 4 hours. Condoms reduce the risk of HPV infection, but are not fully effective. The period between exposure to the infection and the development of a specific lesion is extremely variable, making it virtually impossible for most individuals to determine exactly when, and from whom, they were exposed to the virus.

Studies have shown that prior infection with HPV does not provide females with reliable immunity against subsequent infections or reduce the risk of an HPV infection becoming persistent. Approximately 50% of females generate antibodies against initial HPV infections. In females that do generate anti-HPV antibodies, levels are typically low and slow to develop and are not reliably protective. Since antibody levels in women that have cleared an HPV infection are either low or not-existent, women may be susceptible to the same or different HPV type in the future. In the absence of detectable anti-HPV antibodies, generating immune memory in response to HPV infection in previously exposed women has not been demonstrated to provide protection against future infection or disease.

In Canada, cervical cancer affects females of all ages and among females aged 20 to 44, cervical cancer ranks as second most common to breast cancer. The proportion of HPV-16 and HPV-18 related cervical cancer cases in North America is 76% and increases to 84% when HPV-16, -18, -45, and -31 are included. The annual rate of new diagnoses of cervical cancer in Canada is 8.9/100,000 and the annual mortality rate is 2.5/100,000. The annual rate of new diagnoses of adenocarcinoma of the cervix may be as high as 1.83/100,000 in Canada. Despite the significant reduction in the burden of disease from cervical cancer since the introduction of cervical cancer screening, new cases and deaths from cervical cancer continue, with approximately 1300 new cases and 380 deaths from cervical cancer estimated in 2008.

Infections with multiple oncogenic HPV types are common in sexually active females with cytologic abnormalities; however, almost all cervical cancer is attributable to a single HPV type. Natural history studies of HPV infection support that the risk of progression to cervical precancers and cervical cancers increases with persistent infection. In fact, HPV persistent infections tend to occur at a higher percentage with HPV-16 than with other oncogenic HPV types and that the risk of progression to cervical cancer is higher for HPV-16, -18 and -45 than other HPV types.

Worldwide, the proportion of cervical intraepithelial neoplasia (CIN) grades 2 and 3, and invasive cervical cases associated with HPV-16 and HPV-18 are 52.3% and 70.3% respectively. HPV-16 predominates in squamous cell carcinomas (55.2%) as well as in cervical adenocarcinomas (48.4%), whereas HPV-18 has been detected more than twice as frequently in adenocarcinoma (36.3%) as compared to squamous cervical carcinomas (12.8%).

Overall, incidence and mortality rates due to cervical cancer have shown a steady decline in the past 30 years due to the introduction of Pap screening programs. The reduction has been driven primarily by decreases in the rates of cervical squamous cell carcinomas, the predominant histological type. Rates of adenocarcinoma and adenosquamous carcinomas have increased over this period, particularly in females 20 to 34 years of age. Rates have plateaued in the last 5 years, suggesting that further prevention strategies beyond Pap screening may be necessary. Given that adenocarcinomas occur further in the endocervical canal, they are often more difficult to detect through normal cytological screening.

Until recently, cervical cancer screening programs have allowed for detection and removal of precancerous lesions (secondary prevention). Primary prevention of these lesions via vaccination can provide an additional opportunity to prevent cervical cancer by prevention of the infection which initiates the disease process.

Mechanism of Action

CERVARIX™ is a non-infectious recombinant vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of oncogenic HPV types 16 and 18. Since the VLPs contain no viral DNA, they cannot infect cells, reproduce or cause disease.

High and sustained antibodies against HPV are associated with protection against HPV-related infection and/or disease. Animal studies suggest that the efficacy of L1 VLP vaccines is predominantly mediated by the development of neutralizing antibody (humoral) immune responses. Vaccination with HPV L1 capsid proteins predominately induces serum neutralizing IgG antibodies; however, transudation of anti-HPV IgG neutralizing antibodies from the serum to the cervical mucosa is thought to provide a mechanism to prevent HPV entry into cervical epithelial cells which might otherwise lead to infection and cervical cancer. CERVARIX™ studies have demonstrated that there is a correlation between levels of anti-HPV antibodies in serum samples relative to anti-HPV antibodies in cervicovaginal secretion samples. While the minimum level of antibodies required to prevent HPV infection are not yet known, anti-papillomavirus antibodies have been shown to be sufficient to prevent infection and/or disease. These data suggest that the mechanism of action of L1 VLP vaccines is primarily mediated through a vaccine-induced antibody-mediated immune response.

The adjuvant in CERVARIX™ is AS04 which has been shown in clinical trials to induce a stronger and sustained immune response compared to the same antigens adjuvanted with aluminum salt [Al(OH)₃] alone.

STORAGE AND STABILITY

Store in a refrigerator at 2°C to 8°C. Do not freeze. Store in the original package in order to protect from light.

The expiry date of the vaccine is indicated on the label and packaging. Do not use after the expiry date shown on the label.

CERVARIX™ should be administered as soon as possible after being removed from the refrigerator. However, stability data generated indicated that CERVARIX™ remains stable and can be administered in case the vaccine has been stored outside the refrigerator up to three days at temperatures between 8°C and 25°C or up to one day at temperatures between 25°C and 37°C. If exposed to temperatures >37°C, discard vaccine.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

CERVARIX™ is available as a suspension for injection.

Composition

One dose (0.5 mL) contains:

Human Papillomavirus type 16 L1 protein ²	20 micrograms
Human Papillomavirus type 18 L1 protein ²	20 micrograms
3- <i>O</i> -desacyl-4'-monophosphoryl lipid A (MPL) ³	50 micrograms
aluminum hydroxide, hydrated (Al(OH) ₃) ²	0.5 milligrams Al ³⁺

Additional Excipients

Sodium chloride, sodium dihydrogen phosphate dihydrate, water for injection.

Packaging

Pre-filled Syringes

CERVARIX™ is available 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.

Note: Multiple safety needle tips are compatible with this system.

Vials

CERVARIX™ is available as:

- 0.5 mL of suspension in a vial (type I glass) with a stopper (rubber butyl) in pack sizes of 1, 10 and 100.

Pre-filled syringe components contain latex and vial components are latex-free.

² L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system

³ The GlaxoSmithKline proprietary AS04 adjuvant system is composed of aluminum hydroxide and 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL)

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

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

Product Characteristics

This prophylactic HPV vaccine is composed of HPV-16 and -18 L1 proteins assembled as non-infectious Virus Like Particles (VLP).

CLINICAL TRIALS

Table 5 Summary of Patient Demographics for Clinical Trials in Cervical Disease

Study #	Trial Design	Dosage, route of administration	Study subjects (n=number)	Mean Age (Range)	Gender
HPV-001	Double-blind, randomized, controlled study,	Vaccine: HPV-16/18 L1 20 µg/20 µg	Total n=1113 Vaccine n=560	20.2 (15-25 yrs)	Female
HPV-007		Control: Al(OH) ₃ 500 µg	Control n=553		
	3 yr long term extension of HPV-001	Intramuscular injection 3 doses 0.5 mL	Total n=776 Vaccine n=393 Control n=383	23.2 (17-29 yrs)	
HPV-008	Double-blind, randomized, controlled, multicentre study	Vaccine: HPV-16/18 L1 20 µg/20 µg	Total n=18,665 Vaccine n=9332	20 (15-25 yrs)	Female
		Control: Hep A vaccine	Control n=9333		
		Intramuscular injection 3 doses 0.5 mL			
HPV-012	Blinded, randomized, multicentre study	Vaccine: HPV-16/18 L1 20 µg/20 µg	Total n=870 Vaccine n=612 (15-25 yrs)	19.8-20.3 * (15-25 yrs)	Female
		Control: Hep A vaccine	Control n=258		
		Intramuscular injection 3 doses 0.5 mL	Vaccine n=158 (10-14 yrs)	12.4 (10- 14 yrs)	
HPV-013	Multicentre double- blind, randomized, controlled study	Vaccine: HPV-16/18 L1 20 µg/20 µg	Total n=2067 Vaccine n=1035	12.1 (10-14 yrs)	Female
		Control: Hep A vaccine	Control n=1032		
		Intramuscular injection 3 doses 0.5 mL			
HPV-014	Multicentre open age-stratified study	Vaccine: HPV-16/18 L1 20 µg/20 µg	Total n=666 Vaccine n=229 (15-25 yrs)	34.8 (15-55 yrs)	Female
		Control: Hep A vaccine	Control n=437		
		Intramuscular injection 3 doses 0.5 mL	Vaccine n=226 (26-45 yrs) Vaccine n=211 (46-55 yrs)		

*mean age for 4 lots of CERVARIX™

Vaccine Efficacy

Cervical intraepithelial neoplasia (CIN) grade 2 and 3 lesions or cervical adenocarcinoma *in situ* (AIS) are precursors of squamous cell carcinoma and adenocarcinoma of the cervix, respectively and have been used as a surrogate marker of cervical cancer. CIN2/3 and AIS (precancerous lesions) serve as surrogate markers for the prevention of cervical cancer and were efficacy endpoints used in clinical trials. Secondary endpoints included an assessment of efficacy in the prevention of 6 month persistent infection and 12 month persistent infection.

CERVARIX™ was assessed in 2 double-blind, randomized, controlled clinical studies that included a total of 19,778 females 15 to 25 years of age at enrolment.

Study HPV-001/HPV-007 which was conducted in North America and Latin America, enrolled females who 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 had normal cytology. This represents a population presumed naïve without current HPV infection at the time of vaccination and without prior exposure to either HPV-16 or HPV-18. Females were enrolled in an extended follow-up study (HPV-007) to evaluate the long-term efficacy, immunogenicity, and safety and were followed for up to 6.4 years to date.

Study HPV-008 was conducted in North America, Latin America, Europe, Asia Pacific and Australia. This study enrolled females who were vaccinated regardless of baseline HPV DNA status, serostatus or cytology. These females reflect a general population inclusive of females naïve (without current infection and without prior exposure) or non-naïve (with current infection and/or with prior exposure) to HPV. Before vaccination, cervical samples were assessed for oncogenic HPV DNA (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68) and serostatus of HPV-16 and HPV-18 antibodies. The mean follow-up for this study was approximately 39 months.

In studies HPV-001/HPV-007 and HPV-008 the following endpoints were evaluated:

- Histopathologically-confirmed CIN2+ (CIN2, CIN3, adenocarcinoma *in-situ* (AIS) or invasive cervical cancer) associated with HPV-16 or HPV-18*.
- Histopathologically-confirmed CIN1+ (CIN1, CIN2, CIN3, adenocarcinoma *in-situ* (AIS) or invasive cervical cancer) associated with HPV-16 or HPV-18*.
- Persistent infection (12-month definition[†]) with HPV-16 or HPV-18*.
- Persistent infection (6-month definition[‡]) with HPV-16 or HPV-18.

* These endpoints were not evaluated in study HPV-001, but were evaluated in the extension study HPV-007

† Defined as the detection of the same HPV type at all available time points over approximately a 12 month interval

‡ Defined as the detection of the same HPV type in cervical samples at two consecutive evaluations over approximately a 6-month interval

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)

In both studies, testing for oncogenic HPV types was conducted using SPF10-LiPA25 PCR because of its high sensitivity, specificity and ability to detect degraded HPV DNA in archived biopsy samples. Type-specific HPV-16 and HPV-18 PCR was combined with SPF10-LiPA25 PCR to maintain sensitivity in the context of multiple infections. A high sensitivity for detection of any HPV-16 or HPV-18 DNA even at very low levels

and in the presence of multiple HPV types in both cervical and biopsy samples was important to assure complete case detection.

Prophylactic Efficacy Against HPV Types 16 and 18

Study HPV-008

Study HPV-008 was a double-blind, randomized, controlled clinical trial in which 18,665 healthy females 15 to 25 years of age received CERVARIX™ or Hepatitis A Vaccine control on a 0-, 1-, and 6-month schedule.

In this study, females were vaccinated regardless of baseline HPV DNA status, serostatus or cytology. Females with HPV DNA present at the cervix (HPV DNA positive [DNA(+)]) at study entry were considered currently infected with that specific HPV type. If HPV DNA was not detected by PCR, females were considered HPV DNA negative [DNA(-)]. Additionally, cervical samples were assessed for cytologic abnormalities and serologic testing was performed for anti-HPV-16 and anti-HPV-18 serum antibodies at baseline. Females with anti-HPV serum antibodies present were considered previously exposed to HPV and characterized as seropositive [sero(+)]. Of those, females DNA(-) for HPV-16 and HPV-18 were considered as having cleared a previous natural infection. Females without antibodies to HPV-16 and HPV-18 were characterized as seronegative [sero(-)]. Before vaccination, 73.6% of females were naïve (without current infection and without prior exposure) to HPV-16 and HPV-18.

HPV-008 Study cohorts

According to Protocol (ATP)

The According to Protocol (ATP) cohort for efficacy analysis included:

- all females who received 3 doses of vaccine for whom efficacy endpoint measures were available
- all females who were HPV DNA(-) and sero(-) at baseline for the HPV type considered in the analysis
- all females who were HPV DNA(-) at month 6 for the HPV type considered in the analysis
- normal or low-grade cytology (ASC-US or LSIL) at baseline (females with high-grade cytology were excluded)
- all females who met all eligibility criteria
- all females who complied with procedures defined in the protocol, and
- with no elimination criteria during the study

Total Vaccinated Cohort (TVC)

The total vaccinated cohort (TVC) included:

- all females who received at least 1 dose of the vaccine for whom efficacy endpoint measures were available
- all females were included irrespective of the HPV DNA status and serostatus at baseline

This cohort is representative of a broader population including females with current HPV infection and/or prior exposure.

For analyses of efficacy, case counting in the ATP cohort started on day 1 after the third dose of vaccine and in the TVC cohort, case counting started on day 1 after the first dose.

Clinical Study Results

Study HPV-008

CERVARIX™ was efficacious in the prevention of precancerous lesions or AIS associated with HPV-16 or HPV-18 (Table 6). As many lesions containing HPV-16/18 also contained other oncogenic HPV types, (33 out of the 60 CIN2+ lesions), a type assignment algorithm was applied. For lesions in which multiple HPV types were detected, a blinded, professional-led team, assigned the HPV type most likely responsible for each lesion using HPV type information from the lesion and from prior cytological samples. The algorithm considered the HPV types detected in at least 1 of the 2 preceding cytologic samples, in addition to types detected in the lesion. This analysis excluded 6 cases of CIN2+ (3 cases in the HPV group and 3 cases in the control group) in the ATP cohort and 9 cases of CIN2+ (5 cases in the HPV group and 4 cases in the control group) in the TVC. These cases were not likely to have been caused by the vaccine HPV types to which they were associated according to the original protocol-specified analysis.

Table 6 Efficacy of CERVARIX™ Against Histopathological Lesions Associated with HPV-16 or HPV-18 (HPV Type Assignment Algorithm)

	ATP Cohort [*]			TVC Cohort ^{**}		
	CERVARIX™ N=7344	Control ^a N=7312	% Efficacy (96.1% CI) ^b	CERVARIX™ N=8667	Control ^a N=8682	% Efficacy (96.1% CI) ^b
	Cases	Cases		Cases	Cases	
CIN2/3 or AIS	1	53	98.1 (88.4, 100)	77	170	54.7 (39.5, 66.3)
CIN1/2/3 or AIS	2	90	97.8 (91.4, 99.8)	97	232	58.2 (46.2, 67.8)

^{*} DNA(-) for the corresponding HPV type considered in the analysis at month 0 and month 6, sero(-) for HPV-16/18 at baseline; all 3 doses administered; normal cytology, ASC US or LSIL at baseline.

^{**} At least one dose of vaccine and irrespective of their DNA status and serostatus at baseline.

^a Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 µg Al(OH)₃].

^b The 96.1% confidence interval reflected in this final analysis results from statistical adjustment for the previously conducted interim analysis.

An ATP-generally naïve cohort, which represents a cohort of young women who are presume naïve, was also evaluated. This cohort was similar to ATP, except that the baseline status of the subject was HPV DNA(-) to 14 oncogenic HPV types and the cytology was normal (Table 7).

Table 7 Efficacy of CERVARIX™ Against Histopathological Lesions Associated with HPV-16 or HPV-18 (HPV Type Assignment Algorithm)

	ATP HPV Naïve * ^a		
	CERVARIX™ N=4678	Control ^b N=4580	% Efficacy (96.1% CI) ^c
	Cases	Cases	Cases
CIN2/3 or AIS	0	36	100 (88.7, 100)
CIN1/2/3 or AIS	0	53	100 (92.4, 100)

* DNA(-) for 14 oncogenic types at baseline, sero(-) for HPV-16/18 at baseline, DNA(-) for the corresponding HPV type considered in the analysis at month 6; all 3 doses administered; normal cytology at baseline. Analyses were not pre-specified for this cohort.

^a This data is not representative of the expected vaccinee population.

^b Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 µg Al(OH)₃].

^c The 96.1% confidence interval reflected in this final analysis results from statistical adjustment for the previously conducted interim analysis.

Efficacy against virological endpoints was assessed as persistent infection with oncogenic HPV types is a necessary precursor for precancerous lesions. Efficacy of CERVARIX™ against 12-month persistent infection is presented in Table 8.

Table 8 Efficacy of CERVARIX™ Against Persistent Infection Associated With HPV-16 or HPV-18

HPV-16/18 endpoint	ATP Cohort [*]			TVC Cohort ^{**}		
	CERVARIX™	Control ^a	% Efficacy (96.1% CI) ^b	CERVARIX™	Control ^a	% Efficacy (96.1% CI) ^b
	Cases / N	Cases / N		Cases/N	Cases/N	
Virological endpoint 12-month persistent infection ^c	21 / 7035	233 / 6984	91.2 (85.9, 94.8)	331/8625	620/8648	47.5 (39.5, 54.6)

* DNA(-) for the corresponding HPV type considered in the analysis at month 0 and month 6, sero(-) for HPV-16/18 at baseline; all 3 doses administered; normal cytology, ASC US or LSIL at baseline.

** At least one dose of vaccine and irrespective of their DNA status and serostatus at baseline.

^a Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 µg Al(OH)₃].

^b The 96.1% confidence interval reflected in this final analysis results from statistical adjustment for the previously conducted interim analysis.

^c 12 month persistent infections may regress rather than progress to pre-cancer causing lesions.

Study HPV-001 / Study HPV-007

In a second double-blind, randomized, controlled study (HPV-001), the efficacy of CERVARIX™ in the prevention of HPV-16 or HPV-18 incident and persistent infections was compared with placebo in 1113 females 15 to 25 years of age. The population was naïve to current oncogenic HPV infection or prior exposure to HPV-16 and HPV-18 at the time of vaccination (total cohort). A total of 776 females were enrolled in the extended follow-up study (HPV-007) to evaluate the long-term efficacy, immunogenicity, and safety of CERVARIX™. Subjects were followed for up to 6.4 years to date. Histopathological and virological efficacy data combining Study HPV-001 and the extension Study HPV-007 are presented in Table 9.

Table 9 Efficacy of CERVARIX™ Against Histopathological Lesions and Persistent Infection Associated with HPV-16 or HPV-18 in a Naïve Population up to 6.4 Years

HPV-16/18 endpoint	CERVARIX™	Control (Aluminum salt)	% Efficacy (98.67% CI) ^a
	Cases / N		
Histopathological Endpoints* associated with HPV-16 or HPV-18			
CIN2/3 or AIS ^{***}	0 / 481	9 / 470	100 (28.4, 100)
CIN1/2/3 or AIS ^{***}	0 / 481	15 / 470	100 (62.1, 100)
Virological Endpoints** associated with HPV-16 or HPV-18			
12-month persistent infection ^b	0 / 401	20 / 372	100 (74.4, 100)

*The protocol-specified analysis for histopathological efficacy was the Total Cohort. Cohort included females (including females who had normal cytology at baseline) who received at least one dose of vaccine and were HPV DNA(-) for 14 high risk oncogenic HPV types and sero(-) for both HPV-16 and HPV-18 at baseline.

** Virologic efficacy analyses were performed using the ATP cohort. Cohort included females (including females who had normal cytology at baseline) who received 3 doses of vaccine and were HPV DNA(-) for 14 high risk oncogenic HPV types, sero(-) for both HPV-16 and HPV-18 at baseline and HPV DNA(-) at month 6 for the corresponding HPV type.

*** The analyses of CIN1+ and CIN2+ lesions were secondary objectives of study HPV-007.

^a The 98.67% confidence interval reflected in this final analysis results from statistical adjustment for analyses previously conducted.

^b 12 month persistent infections may regress rather than progress to pre-cancer causing lesions.

In study HPV-001/007, females were followed for efficacy for up to 6.4 years (approximately 77 months) after dose one.

Efficacy in Females Regardless of Prior Exposure to HPV-16 or HPV-18 and Serostatus at Baseline (Study HPV-008)

Table 10 Efficacy of CERVARIX™ in Females Regardless of Prior Exposure to HPV-16 or HPV-18 in the TVC cohorts (HPV Type Assignment Algorithm)

	TVC Cohort*		
	CERVARIX™	Control ^a	% Efficacy (96.1% CI) ^b
	Cases / N	Cases / N	
DNA -/Sero - at baseline			
CIN2/3 or AIS	2/8079	88/8112	97.7 (91.1, 99.8)
DNA -/Sero + at baseline			
CIN2/3 or AIS	1/1710	9/1777	88.5 (10.8, 99.8)
DNA +/Sero - at baseline			
CIN2/3 or AIS	20/309	28/293	32.8 (-27.4, 65.3)
DNA +/Sero + at baseline			
CIN2/3 or AIS	53/333	44/307	-13.8 (-77.6, 26.7)

* At least one dose of vaccine and irrespective of their DNA status and serostatus at baseline.

^a Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 µg Al(OH)₃].

^b The 96.1% confidence interval reflected in this final analysis results from statistical adjustment for the previously conducted interim analysis.

In females who were DNA(-) and sero(-) for HPV-16 or HPV-18, efficacy against CIN2/3 or AIS associated with HPV-16 or HPV-18 in the TVC cohort was 97.7% (96.1% CI: 91.1, 99.8). Vaccine efficacy analyses were performed in females who were DNA(-) and sero(+) for HPV-16 or HPV-18 with the objective to understand the potential benefit of vaccination in females who have had evidence of previous exposure but not currently infected. Vaccine efficacy against CIN2/3 or AIS associated with HPV-16 or HPV-18 in this cohort was 88.5% (96.1% CI: 10.8, 99.8). In two small subgroups of females with evidence of current infection (DNA +/sero - and DNA +/sero +), a benefit from vaccination was not evident (see Table 10).

Efficacy Results for Non-Vaccine Oncogenic HPV Types

In study HPV-008, post-hoc analyses for vaccine efficacy, adjusted for multiplicity, were conducted in the ATP and TVC cohorts to assess the impact of CERVARIX™ on CIN2/3 or AIS due to 12 non-vaccine oncogenic HPV types (HPV-31, -33, -35, -39, -45,-51, -52, -56, -58, -59, -66, - 68).

The ATP cohort for these analyses included all subjects irrespective of serostatus who received 3 doses of CERVARIX™ and were DNA negative for the specific HPV type at baseline and month 6. The TVC cohort for these analyses included all females irrespective of the HPV DNA status and serostatus at baseline, who received at least 1 dose of the vaccine and for whom efficacy endpoint measures were available. Vaccine

efficacy in prevention of CIN2/3 or AIS associated with HPV-31 was 91.3% (99.7% CI: 43.7, 99.8) in the ATP cohort. Vaccine efficacy in prevention of CIN2/3 or AIS associated with HPV-45 was 100.0% (99.7% CI: 29.0, 100.0) in the TVC cohort (see Table 11).

Table 11 Efficacy of CERVARIX™ Against Non-vaccine Oncogenic HPV Types for CIN2/3 or AIS (ATP and TVC cohorts) (HPV Type Assignment Algorithm)

HPV type	ATP Cohort [†] (CIN2/3 or AIS [*])			TVC Cohort ^{**} (CIN2/3 or AIS [*])		
	CERVARIX™	Control ^a	% Efficacy (99.7% CI) ^b	CERVARIX™	Control ^a	% Efficacy (99.7% CI) ^b
	Cases / N	Cases / N		Cases / N	Cases / N	
HPV-16 related types^{††}						
HPV-31	2/7583	23/7599	91.3 ^c (43.7, 99.8)	28/8667	46/8682	38.9 (-25.2, 71.4)
HPV-33	7/7720	22/7706	68.1 (-12.0, 93.4)	24/8667	43/8682	44.0 (-20.1, 75.2)
HPV-35	1/7768	4/7764	74.9 (-526.2, 100.0)	6/8667	10/8682	39.8 (-201.7, 90.4)
HPV-52	12/7461	11/7414	-9.1 (-326.0, 71.4)	36/8667	33/8682	-9.5 (-131.4, 47.8)
HPV-58	6/7709	16/7702	62.3 (-54.2, 93.5)	20/8667	28/8682	28.3 (-75.3, 71.9)
HPV-18 related types^{††}						
HPV-39	3/7609	7/7614	56.9 (-254.9, 97.4)	10/8667	14/8682	28.3 (-161.1, 82.0)
HPV-45	0/7782	4/7745	100.0 (-298.4, 100.0)	0/8667	12/8682	100.0 ^c (29.0, 100.0)
HPV-59	1/7720	3/7723	66.5 (-1131.3, 100.0)	5/8667	5/8682	-0.4 (-804.9, 88.9)
HPV-68	4/7633	8/7614	49.9 (-233.1, 95.2)	8/8667	15/8682	46.5 (-102.7, 88.3)
Other types^{††}						
HPV-51	10/7363	25/7352	59.9 (-20.8, 89.0)	24/8667	50/8682	51.9 (-0.5, 78.4)
HPV-56	3/7646	7/7638	57.0 (-254.0, 97.4)	6/8667	17/8682	64.6 (-41.9, 93.8)
HPV-66	4/7592	9/7564	55.5 (-175.6, 95.6)	10/8667	18/8682	44.3 (-84.7, 85.4)

[†] DNA(-) for the corresponding HPV type in the analysis at month 0 and month 6, irrespective of serostatus, all 3 doses administered.

^{††} Types are listed in numerical order and not according to epidemiological data.

^{*} These analyses only considered the detection of DNA for the HPV type evaluated and did not consider the presence or absence of DNA of other HPV types in the lesions; therefore, a proportion of lesions had DNA detected for multiple HPV types.

^{**} At least one dose of vaccine and irrespective of their DNA status and serostatus at baseline.

^a Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 µg Al(OH)₃].

^b The 99.7% confidence interval reflected in this final analysis is based on adjusted alpha calculated with Bonferroni method (the alpha allocated to the final analysis was divided by 12; the number of oncogenic HPV types excluding HPV-16 and HPV18 resulting in an alpha equal to 0.325%).

^c Statistically significant vaccine efficacy against CIN2/3 or AIS.

Overall Efficacy of CERVARIX™ on HPV Disease Burden

In the TVC population, vaccine efficacy against CIN2/3 or AIS was 30.4% (96.1% CI: 16.4, 42.1) in all females regardless of HPV DNA type in the lesion. In the TVC population, vaccine efficacy against CIN1/2/3 or AIS, CIN2/3 or AIS, and CIN3 or AIS was demonstrated in all females regardless of HPV DNA type in the lesion (Table 12).

Table 12 Efficacy of CERVARIX™ Against Histopathological Lesions Irrespective of HPV DNA Type in the Lesion, and HPV DNA Status and Serostatus at Baseline (TVC)

		CERVARIX™	Control ^a	% Efficacy (96.1% CI) ^b
		Cases / N	Cases / N	
CIN2/3 or AIS	Irrespective of HPV DNA at Baseline*	224 / 8667	322 / 8682	30.4 (16.4, 42.1)
CIN3 or AIS	Irrespective of HPV DNA at Baseline*	77 / 8667	116 / 8682	33.4 (9.1, 51.5)
CIN1/2/3 or AIS	Irrespective of HPV DNA at Baseline*	451 / 8667	577 / 8682	21.7 (10.7, 31.4)

* TVC which includes all vaccinated females (who received at least one dose of vaccine) irrespective of HPV DNA status and serostatus at baseline.

^a Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 µg Al(OH)₃].

^b The 96.1% confidence interval reflected in this final analysis results from statistical adjustment for the previously conducted interim analysis.

In a sub-analysis of the population naïve to oncogenic HPV (TVC naïve), CERVARIX™ was also efficacious against CIN1/2/3 or AIS, CIN2/3 or AIS, and CIN3 or AIS regardless of the HPV DNA type in the lesion (Table 13).

Table 13 Efficacy of CERVARIX™ Against Histopathological Lesions - HPV DNA(-) for 14 Oncogenic HPV Types and Sero(-) for HPV-16 and HPV-18 at Baseline (TVC naïve)

		CERVARIX™	Control ^a	% Efficacy (96.1% CI) ^b
		Cases / N	Cases / N	
CIN2/3 or AIS	Prophylactic Efficacy [*]	33 / 5449	110 / 5436	70.2 (54.7, 80.9)
CIN3 or AIS	Prophylactic Efficacy [*]	3 / 5449	23 / 5436	87.0 (54.9, 97.7)
CIN1/2/3 or AIS	Prophylactic Efficacy [*]	106 / 5449	211 / 5436	50.1 (35.9, 61.4)

^{*} TVC naïve which includes all vaccinated females (who received at least one dose of vaccine) who had negative cytology, were HPV DNA(-) for 14 oncogenic HPV types and sero(-) for HPV-16 and HPV-18 at baseline.

^a Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 µg Al(OH)₃].

^b The 96.1% confidence interval reflected in this final analysis results from statistical adjustment for the previously conducted interim analysis.

Pregnancy Outcomes

There are no adequate and well-controlled studies in pregnant women. Pregnancy testing was performed prior to each vaccine administration and vaccination was discontinued in case of a positive pregnancy test. In all clinical trials, females were instructed to take precautions to avoid pregnancy until 2 months after the last vaccination.

Table 14 Pregnancy Outcomes Overall for the Total Number of Pregnancies in Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023 (TVC)

Pregnancy outcomes	CERVARIX™*		Pooled Control**		Total	
	N = 3696		N = 3580		N = 7276	
	n	%	n	%	n	%
Normal Infant	2300	62.23	2240	62.57	4540	62.40
Premature birth	73	1.98	62	1.73	135	1.86
Abnormal infant other than congenital anomaly	105	2.84	114	3.18	219	3.01
Elective termination	216	5.84	217	6.06	433	5.95
Therapeutic abortion	4	0.11	4	0.11	8	0.11
Ectopic pregnancies	22	0.60	21	0.59	43	0.59
Spontaneous abortion	408	11.04	388	10.84	796	10.94
Still birth	20	0.54	19	0.53	39	0.54
Congenital anomaly	30	0.81	28	0.78	58	0.80
Lost to follow-up	24	0.65	25	0.70	49	0.67
Not applicable	4	0.11	3	0.08	7	0.10
Pregnancy ongoing	490	13.26	459	12.82	949	13.04

* HPV-16/18 vaccine group (Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023).

** Pooled Control = Al(OH)₃, Hepatitis A control group containing 360 EL.U. hepatitis A antigen per dose and Hepatitis A control group containing 720 EL.U. hepatitis A antigen per dose.

Notes:

Twin pregnancies counted as one pregnancy, Spontaneous abortion includes missed abortion, Not applicable: e.g. mole, trophoblastic tumor.

Outcomes Around Time of Vaccination

Sub-analysis were conducted to describe pregnancy outcomes in 761 women who had their last menstrual period within 30 days prior to, or 45 days after a vaccine dose and for whom pregnancy outcome was known (Table 15).

Table 15 Pregnancy Outcomes Around Vaccination for the Total Number of Pregnancies in Studies HPV-001, 003, 004, 005, 008, 009, 012, 013, 014, 015, 016 (TVC)

Pregnancy outcomes	CERVARIX™* N = 396		Pooled Control** N = 365		Total N = 761	
	n	%	n	%	n	%
Normal Infant	258	65.15	253	69.32	511	67.15
Premature birth	10	2.53	9	2.47	19	2.50
Abnormal infant other than congenital anomaly	20	5.05	17	4.66	37	4.86
Elective termination	39	9.85	35	9.59	74	9.72
Therapeutic abortion	1	0.25	1	0.27	2	0.26
Ectopic pregnancies	2	0.51	1	0.27	3	0.39
Spontaneous abortion	54	13.64	35	9.59	89	11.70
Still birth	1	0.25	3	0.82	4	0.53
Congenital anomaly	7	1.77	5	1.37	12	1.58
Lost to follow-up	4	1.01	5	1.37	9	1.18
Not applicable	0	0.00	0	0.00	0	0.00
Pregnancy ongoing	0	0.00	1	0.27	1	0.13

* HPV-16/18 vaccine group (Studies HPV-001, 003, 004, 005, 008, 009, 012, 013, 014, 015, 016)

** Pooled Control = Al(OH)₃, Hepatitis A control group containing 360 EL.U. hepatitis A antigen per dose and Hepatitis A control group containing 720 EL.U. hepatitis A antigen per dose.

Notes:

Pregnancies around-vaccinations: Pregnancy in subjects for which their last menstrual period occurred between 30 days before and 45 days after vaccination (pregnancies with missing date of last menstrual period are not included). Twin pregnancies counted as one pregnancy, Spontaneous abortion includes missed abortion, Not applicable: e.g. mole, trophoblastic tumor.

Vaccine-Induced Immunogenicity

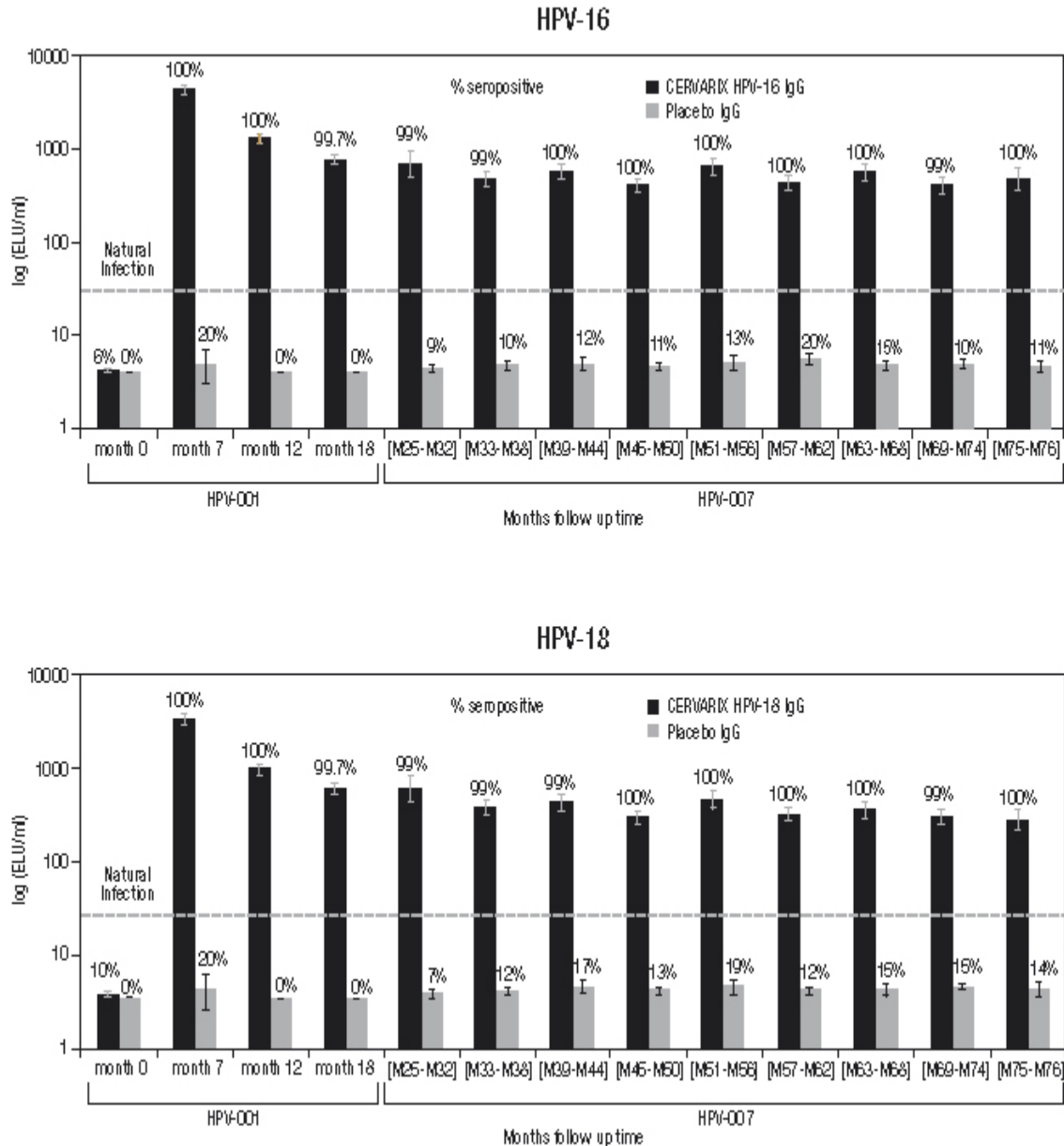
The WHO states that neutralizing antibodies are the likely mediator of protection. CERVARIX™ induced an antibody response to HPV-16 and HPV-18 that was measured using a type specific binding ELISA and PBNA, both of which show strong correlations with each other.

Because the scales for these assays are unique to each HPV type, biologically relevant benchmarks were determined using the antibody response in females who had successfully cleared a previous HPV infection prior to enrollment, and had mounted an immune response to natural infection (i.e., HPV DNA(-) and sero(+) for HPV-16 or HPV-18 at baseline). These benchmark antibody levels against HPV-16 and HPV-18 (Study HPV-008) were determined by ELISA to be 29.8 EL.U./mL and 22.6 EL.U./mL, respectively (see natural infection line in Figure 1). For PBNA, the antibody levels against HPV-16 and HPV-18 were 180.1 ED₅₀ and 137.3 ED₅₀, respectively. The minimum levels of antibodies (correlate of protection) required to prevent HPV infection are not yet known. However, antibody levels generated by natural infection may not protect against subsequent infections with the same or different HPV type.

Level and Duration of Immune Response

The immune response against HPV-16 and HPV-18 was evaluated up to 76 months (6.4 years) post-dose 1, in Study HPV-001 and Study HPV-007 in females 15 to 25 years of age at the time of vaccination (Figure 1). Greater than 99% of females remained sero(+) for both HPV-16 and HPV-18 at each time point over 76 months.

Figure 1 Persistence of Anti-HPV-16 and Anti-HPV-18 Antibodies (type specific ELISA) (ATP Cohort for Immunogenicity)



Vaccine-induced GMTs for both HPV-16 and HPV-18 peaked at month 7 and thereafter reached a plateau that was sustained from month 18 up to month 76. For both HPV-16 and HPV-18, GMTs were at least 11-fold higher than titers observed for natural infection at the end of the follow-up period.

In Study HPV-008, geometric mean titers (GMTs) for ELISA and PBNA one month post-dose 3 were measured (Table 16). The ATP cohort for immunogenicity included all evaluable subjects for whom data concerning immunogenicity endpoint measures were available. These included females for whom assay results were available for antibodies against at least one vaccine type. Females who acquired either HPV-16 or HPV-18 infection during the trial were excluded. Of females sero(-) at baseline, 99.5% were sero(+) for anti-HPV-16 and anti-HPV-18 antibodies at month 7 post-vaccination.

Table 16 Summary of Anti-HPV Geometric Mean Titers for HPV-16 and HPV-18 for Initially Sero(-) Females (ATP for Immunogenicity)

	N	CERVARIX™ GMT (95% CI)	N	Control GMT (95% CI)
ELISA* (EL.U./mL)				
Anti-HPV-16	861	9206.4 (8607.2, 9847.2)	738	4.4 (4.2, 4.6)
Anti-HPV-18	924	4744.6 (4454.1, 5053.9)	769	3.8 (3.6, 3.9)
PBNA** (ED₅₀)				
Anti-HPV-16	46	27,364.8 (19,780.1,37,857.9)	44	20.0 (20.0, 20.0)
Anti-HPV-18	46	9052 (6851.8, 11,960.5)	44	20.0 (20.0, 20.0)

N = number of females with pre-vaccination results available; GMT = geometric mean titer.

* Enzyme linked immunosorbent assay (assay cut-off 8 EL.U./mL for anti-HPV-16 antibody and 7 EL.U./mL for anti-HPV-18 antibody).

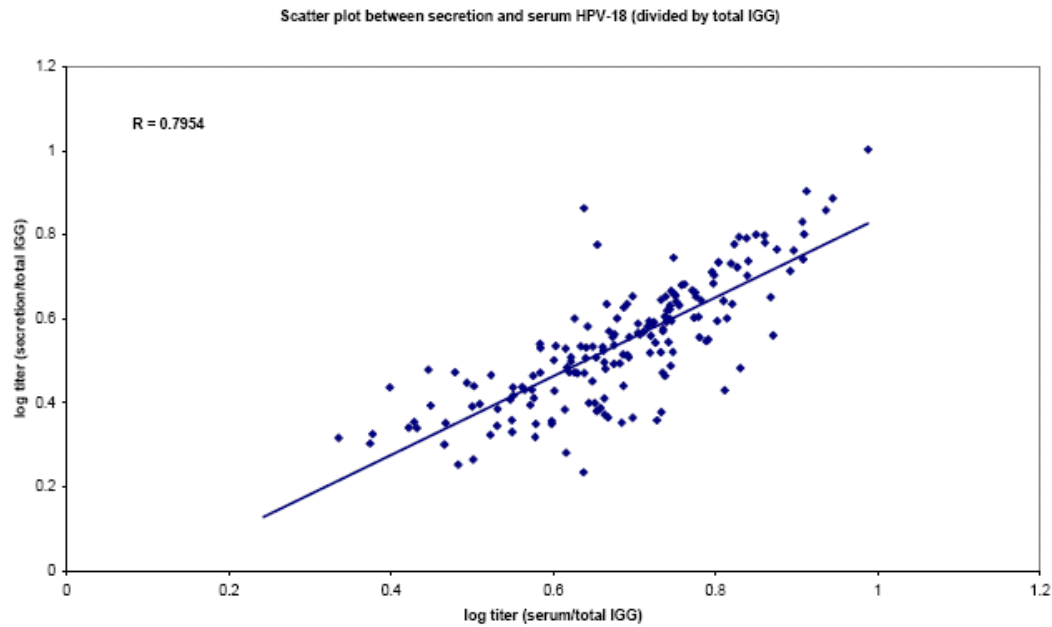
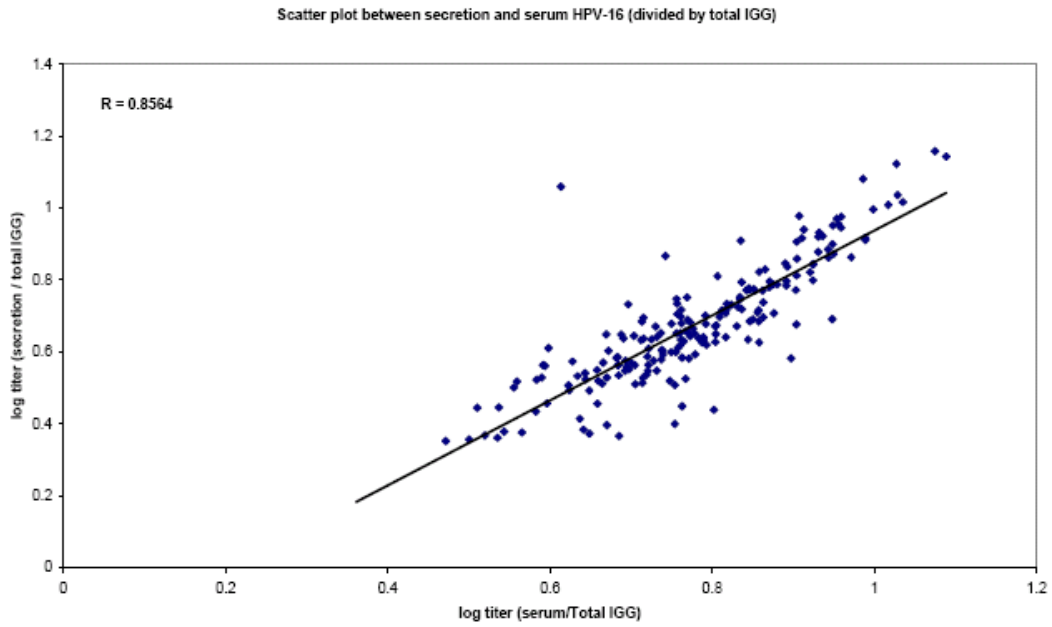
** Pseudovirion Based Neutralization Assay (assay cut-off 40 ED₅₀ for both anti-HPV-16 antibody and anti-HPV-18 antibody).

CERVARIX™ induces a high level of antibodies in the serum relative to natural infection out to 6.4 years. (HPV-001/007, see Figure 1).

Cervicovaginal secretions (CVS) were evaluated from a subset of vaccinees in two studies for anti-HPV-16 IgG and anti-HPV-18 IgG antibodies. In Study HPV-005, the presence and level of antibodies in the CVS were shown to be well correlated to serum antibodies, suggesting that the specific HPV-L1 IgG antibodies detected in the CVS result from transudation to the site of infection.

Transudation of anti-HPV IgG antibodies from serum to the cervical mucosa has been demonstrated in clinical trials (Study HPV-014) in a linear fashion (Figure 2). Higher levels of antibodies in the serum correlate to higher levels of antibodies in the cervicovaginal secretions.

Figure 2 Correlation between serum and cervicovaginal secretion for HPV-16 and HPV-18, standardized for total IgG, all cervicovaginal secretion samples (Total Vaccinated Cohort Extension Month 24)



Bridging of Efficacy of CERVARIX™ from Young Adult Women to Adolescent Girls

The immunogenicity of CERVARIX™ was evaluated in 2 clinical studies involving 1193 females 10 to 14 years of age who received CERVARIX™. Efficacy in females less than 15 years of age was assessed by comparing immunogenicity data from females 15 to 25 years of age.

Study HPV-013 was a double-blind, randomized, controlled study in which 1035 females received CERVARIX™ and 1032 females received a Hepatitis A Vaccine as the control vaccine with a subset of females evaluated for immunogenicity. All initially sero(-) females in the group who received CERVARIX™ seroconverted to both HPV-16 and HPV-18 antigens after vaccination. The GMTs for anti-HPV-16 and anti-HPV-18 antibodies in initially sero(-) females are presented in Table 17. At Month 24, 99.8% of the subjects remained sero(+) for anti-HPV-16 antibodies and all subjects (100%) remained sero(+) for anti-HPV-18 antibodies.

Table 17 Geometric Mean Titers for Initially Sero(-) Females 10 to 14 Years of Age (ATP Cohort for Immunogenicity)

Anti-HPV-16 Antibodies GMT EL.U./mL (95% CI)			Anti-HPV-18 Antibodies GMT EL.U./mL (95% CI)		
Month 7 N=519	Month 18 N=518	Month 24 N=517	Month 7 N=526	Month 18 N=525	Month 24 N=525
19,882.0 (18,600.3, 21,466.4)	3910.1 (3612.7, 4232.0)	3198.0 (2952.8, 3463.6)	8248.6 (7658.6, 8884.1)	1539.4 (1414.4, 1675.4)	1251.3 (1152.7, 1358.3)

N = number of females with pre-vaccination results available; GMT = geometric mean titer.

In Study HPV-012, the immunogenicity of CERVARIX™ administered to females 10 to 14 years of age was compared to that in females 15 to 25 years of age. The immune response (seroconversion) in females 10 to 14 years of age measured post-dose 3 was 100% for both HPV-16 and HPV-18 antigens and was non-inferior to that seen in females 15 to 25 years of age (Table 18). The anti-HPV-16 and anti-HPV-18 GMTs in the 10- to 14-year age group were more than 2-fold higher than in the 15- to 25-year age group.

Table 18 Geometric Mean Titers for Initially Sero(-) Females 10 to 14 Years Compared to 15 to 25 Years of Age (ATP Cohort for Immunogenicity)

	10 to 14 Years of Age			15 to 25 Years of Age		
	N	GMT* EL.U./mL (95% CI)	Seropositivity Rate %** (95% CI)	N	GMT* EL.U./mL (95% CI)	Seropositivity Rate %** (95% CI)
Anti-HPV-16	143	17,272.5 (15,117.9, 19,734.1)	100	118	7438.9 (6324.6, 8749.6)	100
Anti-HPV-18	141	6863.8 (5976.3, 7883.0)	100	116	3070.1 (2600.0, 3625.4)	100

N = number of females with pre-vaccination results available; GMT = geometric mean titer.

* Non-inferiority based on the upper limit of the 2-sided 95% CI for the GMT ratio (15-25 year olds/10-14 year olds) was <2.

** Non-inferiority based on the upper limit of the 2-sided 95% CI for the difference between the seropositivity rates for 10-14 year olds and 15-25 year olds was <10%.

Based on these immunogenicity data, the efficacy of CERVARIX™ is inferred in females 10 to 14 years of age.

TOXICOLOGY

Animal toxicology and/or pharmacology

Non-clinical data reveal no special hazard for humans based on conventional studies of acute and repeated dose toxicity, local tolerance and cardiovascular/respiratory safety pharmacology.

Carcinogenesis and Mutagenesis

No studies were done on CERVARIX™. However, the MPL adjuvant was not mutagenic in standard mutagenicity tests.

Reproductive Toxicology

Animal studies performed with CERVARIX™ administered to female rats do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/fetal development, parturition or postnatal development.

The effect of CERVARIX™ on embryo-fetal, peri-natal and post-natal survival and development has been assessed in rats. Such animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/fetal development, parturition or post-natal development.

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PART III: CONSUMER INFORMATION

CERVARIX™

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

This leaflet is part III of a three-part "Product Monograph" published when CERVARIX™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CERVARIX™. Contact your health professional if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:

CERVARIX™ is a vaccine intended to protect females against cervical cancer (cancer of the lower part of the uterus or womb) and abnormal and precancerous cervical lesions (changes in cells of the cervix that have a risk of turning into cancer). These diseases are caused by infection with Human Papillomaviruses (HPV) types 16 and 18 and other cancer causing types.

HPV-16 and HPV-18 are responsible for approximately 70% of cervical cancers cases. Other HPV types can also cause cervical cancer. CERVARIX™ provides protection against HPV-16 and HPV-18, although it will not prevent all cancers or precancerous lesions caused by these or other types of HPV.

What it does:

CERVARIX™ works by stimulating the production of antibodies against HPV types 16 and 18. These antibodies have been shown in clinical trials to protect females aged 15 to 25 years against HPV-16 and HPV-18 related diseases. In 10 to 14 year old girls, the antibodies produced indicate that they will provide just as much protection as in older women.

- CERVARIX™ is not infectious and so, it cannot cause HPV related diseases.
- CERVARIX™ will not treat HPV related diseases already present at time of vaccination.
- If you are currently infected with an HPV-16 or HPV-18 infection, CERVARIX™ may protect you against the other vaccine type.
- CERVARIX™ will not protect against diseases that are caused by other infections, including other types of HPV.

As with all vaccines, CERVARIX™ may not fully protect all people who are vaccinated. It is not a substitute for regular cervical screening and you should continue to consult your health professional for regular cervical cancer screening (i.e. Pap tests).

What is the Adjuvant

An adjuvant is a component added to a vaccine to improve the immune response by providing stronger and longer protection.

Adjuvants have been used in vaccines for almost 80 years. Nearly all vaccines are made with adjuvants. Most common vaccines are designed with traditional adjuvants such as aluminum salts (alum).

The adjuvant system in CERVARIX™ is AS04 which is made up of 1) a natural compound which comes from a type of organism which most people have been exposed to and 2) alum.

Long-Term Protection

In clinical trials, sustained protection has been observed for up to 6.4 years after the first dose. Long-term studies are ongoing to establish the duration of protection.

What is Human Papillomavirus (HPV)?

HPV is a common virus which affects humans. The virus is generally spread by skin-to-skin contact during sexual activity. In most cases, females infected with HPV will not have any symptoms and their body will clear the virus. However, the body does not develop long term protection against HPV and must continue to clear new and previously encountered HPV types. Up to 80% of sexually active females will be infected with HPV during their lifetime, which in some cases may cause cervical cancer.

What is cervical cancer?

Cervical cancer is a serious and sometimes life threatening disease. Cervical cancer is caused by HPV infection. There are about 15 types of HPV that cause most cases of cervical cancer. These HPV types can cause the normal cells on the cervix to turn into abnormal precancerous cervical lesions. If left untreated, some of these lesions can turn into cancer over time. Cervical cancer affects females of all ages and among females aged 20 to 44, cervical cancer ranks as the second most common cancer after breast cancer. Cervical cancer screening (i.e. Pap tests) can identify abnormal changes in the cervix that may be treated.

When it should not be used:

Please see Warnings and Precautions section.

What the medicinal ingredient is:

CERVARIX™ contains Human Papillomavirus type 16 L1 protein and Human Papillomavirus type 18 L1 protein as active substances and is adjuvanted with AS04 adjuvant system [composed of aluminum hydroxide, hydrated and 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL)]. The adjuvant system is designed to boost the body's response to CERVARIX™ leading to long lasting antibody levels. The duration of protection has not been established.

CERVARIX™ is not infectious and so, it cannot cause HPV related diseases.

What the important nonmedicinal ingredients are:

CERVARIX™ contains the following nonmedicinal ingredients: sodium chloride, sodium dihydrogen phosphate dihydrate, and sterile water for injections.

What dosage forms it comes in:

CERVARIX™ is available as:

- 0.5 mL single-dose pre-filled syringe
- 0.5 mL single-dose vial

WARNINGS AND PRECAUTIONS

CERVARIX™ should not be given if you have previously had any allergic reaction to CERVARIX™, or any ingredient contained in CERVARIX™. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

Before you are vaccinated, talk to your health professional if you:

- have a severe infection with a high temperature. It is recommended to delay the vaccination where there is a severe infection or fever until recovery. A minor infection such as a cold should not be a problem, but talk to your health professional first.
- have a bleeding problem or bruise easily

Use in children

CERVARIX™ can be used in children as young as 10 years of age.

Use in pregnancy

Health professionals need to assess the benefits and potential risks of administering the vaccine to pregnant females.

In clinical studies, there was a slightly higher rate of spontaneous abortions in pregnancies which occurred around the time of vaccination in women who were given the CERVARIX™ vaccine compared with those who received a control vaccine. It is not known if this imbalance is due to CERVARIX™.

If pregnancy occurs during the course of vaccination, it is recommended to postpone vaccination until after pregnancy. It is also recommended to take adequate precautions to avoid pregnancy for 2 months following vaccination with CERVARIX™.

Patients and healthcare providers are encouraged to report any exposure to CERVARIX™ vaccine during pregnancy by calling 1-800-387-7374.

Use in breastfeeding

Health professionals need to assess the benefits and potential risks of administering the vaccine to breastfeeding females.

INTERACTIONS WITH THIS VACCINE

If CERVARIX™ is to be given at the same time as another injectable vaccine(s), the vaccines should always be given with separate syringes and at different injection sites.

CERVARIX™ may not have an optimal effect if used with medicines that suppress the immune system.

In clinical trials, oral contraceptives (e.g. the pill) did not reduce the protection obtained by CERVARIX™.

Please tell your health professional if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or have recently received any other vaccine.

PROPER USE OF THIS VACCINE

Usual dose:

Your health professional will give CERVARIX™ as an injection into the muscle. You or your daughter will receive a total of three injections to be given as follows:

- First injection: at chosen date by you and your health professional
- Second injection: 1 month after first injection
- Third injection: 6 months after first injection

If necessary, the vaccination schedule can be more flexible. Please speak to your health professional for more information.

Missed Dose:

It is important that you follow the instructions of your health professional regarding return visits. If you forget to go back to your health professional at the scheduled time, ask your health professional for advice.

If you do not finish the entire vaccination course of three injections, your protection from developing cervical cancer may be reduced.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, CERVARIX™ may cause side effects, although not everybody gets them.

You may feel:

- pain or discomfort at the injection site

or you may see some:

- redness or swelling at the injection site.

However, these effects usually clear up within a few days.

Other side effects that occurred during clinical trials with CERVARIX™ were as follows:

Very common (these may occur with more than 1 in 10 doses of the vaccine):

- headache
- aching muscles, muscle tenderness or weakness, not caused by exercise
- fatigue

Common (these may occur with up to 1 in 10 doses of the vaccine):

- gastrointestinal symptoms including nausea, vomiting, diarrhea and abdominal pain
- itching, red skin rash, hives
- joint pain
- fever ($\geq 38^{\circ}\text{C}$)

Uncommon (these may occur with up to 1 in 100 doses of the vaccine):

- upper respiratory tract infection
- dizziness
- other injection site reactions such as hard lump, tingling or numbness

Rare (these may occur with up to 1 in 1,000 doses of the vaccine):

- Allergic reactions. These can be recognized by:
 - Itchy rash of the hands and feet
 - Swelling of the eyes and face
 - Difficulty in breathing or swallowing
 - Sudden drop in blood pressure and loss of consciousness

These reactions will usually occur a short time after vaccination. However, if you experience any of these symptoms you should contact a doctor immediately.

This is not a complete list of side effects. For any unexpected effects while taking CERVARIX™, contact your health professional.

HOW TO STORE IT

- Keep out of the reach and sight of children.
- Do not use CERVARIX™ after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
- Store in a refrigerator ($2^{\circ}\text{C} - 8^{\circ}\text{C}$).
- Do not freeze.
- Store in the original package in order to protect from light.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects information on serious and unexpected adverse events following vaccination. If you suspect you have had a serious or unexpected event following receipt of a vaccine you may notify the Public Health Agency of Canada:

By toll-free telephone: 1-866-844-0018

By toll-free fax: 1-866-844-5931

Web Address: <http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php>

By regular mail:

Vaccine Safety

130 Colonnade Road

Ottawa, Ontario

K1A 0K9 Address Locator 6502A

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

Patients can refer to www.cervarix.ca for further information.

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.gsk.ca> or by contacting the sponsor,

GlaxoSmithKline Inc.

7333 Mississauga Road

Mississauga, Ontario

L5N 6L4

1-800-387-7374

This leaflet was prepared by GlaxoSmithKline Inc.

Last revised: February 3, 2010

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