Cervarix®

human papillomavirus vaccine types 16 and 18 (recombinant, AS04 adjuvanted)

Active Immunizing Agent

GlaxoSmithKline

Date of Revision: November 25, 2014

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	3-0-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 3-0-desacyl-4'-monophosphoryl lipid A (MPL) adsorbed onto aluminum (as hydroxide salt).

INDICATIONS AND CLINICAL USE: CERVARIX is a vaccine indicated in females from 9 to 45 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

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.

Except for asymptomatic human immunodeficiency virus (HIV) infected individuals for whom limited data are available, there are no data on the use of CERVARIX in individuals with impaired immune responsiveness such as patients receiving immunosuppressive treatment. For those individuals an adequate immune response may not be elicited. The duration of protection has not been established.

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.

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 (LMP) within 30 days prior to, or 45 days after a vaccine dose and for whom pregnancy outcome was known, spontaneous abortion (SA) occurred in a higher proportion of women who received CERVARIX (13.6%) compared to those receiving a control substance (9.6%).

In a post-approval observational study, the relative risk of SA was assessed in women aged 15 to 25 years who received CERVARIX around their LMP (within 30 days prior to, or 45 days after any dose of CERVARIX) compared to women not exposed during this time period (LMP within 120 days to 18 months after their last dose of CERVARIX). The rate of SA for the exposed cohort was 11.6% compared to 9.0% in the non-exposed cohort. These estimated risks are aligned with the overall risk of SA in the general population. In a sensitivity analysis performed, there was an increased risk of SA detected for women exposed to 2 doses of CERVARIX, however the results were inconclusive when considered in conjunction with a larger pooled clinical trial analysis. There was no increased risk of SA in women who received any single CERVARIX dose during the risk period.

Overall, the data is insufficient to conclude if these outcomes are due to a vaccine related effect.

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 9 years of age (see Adverse Reactions). Safety and effectiveness in pediatric patients younger than 9 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

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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 ≥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: CERVARIX
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[b] (10–25 yrs) %	HAV 720[c] (15–25 yrs) %	HAV 360[d] (10–14 yrs) %	$Al(OH)_3$ Control[e] (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[f]	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[g]	49.1	44.9	33.1	—
Arthralgia[g]	20.8	17.9	19.9	—
Urticaria[g]	7.4	7.9	5.4	—

[a] Total vaccinated cohort included subjects with at least one documented dose (N).
[b] 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).
[c] HAV 720=Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 µg $Al(OH)_3$].
[d] HAV 360=Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 µg of $Al(OH)_3$].
[e] $Al(OH)_3$ Control=control containing 500 µg $Al(OH)_3$.
[f] GI=Gastrointestinal symptoms, including nausea, vomiting, diarrhea, and/or abdominal pain.
[g] Adverse events solicited in a subset of subjects.
Legend: Studies: HPV-001, 008 diary card subset, 012, 013, 014, 016.

Table 2: CERVARIX
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])

	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		
Adverse Reaction	**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.

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Table 3: CERVARIX
Rates of Unsolicited Adverse Events in Females 10 Through 25 Years of Age Within 30 Days of Vaccination (≥1% For CERVARIX and Greater Than HAV 720, HAV 360, or $Al(OH)_3$ Control) (Total Vaccinated Cohort[a])

Adverse Event	CERVARIX[b] % N=6654	HAV 720[c] % N=3186	HAV 360[d] % N=1032	$Al(OH)_3$ Control[e] % 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] 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.
[c] HAV 720=Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 µg $Al(OH)_3$].
[d] HAV 360=Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 µg of $Al(OH)_3$].
[e] $Al(OH)_3$ Control=control containing 500 µg $Al(OH)_3$.

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: CERVARIX
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) n (%)[b]	Pooled Control Group[c] (N=10 730) n (%)[b]
Total Number of Subjects with at Least One Medical Condition	**95 (0.8)**	**87 (0.8)**
Arthritis[d]	9 (0.1)	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)

(cont'd)

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Table 4: CERVARIX *(cont'd)*
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) n (%)[b]	Pooled Control Group[c] (N=10 730) n (%)[b]
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] n (%): number and percentage of subjects with medical condition.
[c] 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 $Al(OH)_3$.
[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.

Studies in Females 9 Years of Age: In clinical trials, comparable results were found between the safety and reactogenicity in 9 year old subjects and subjects aged 10 to 14 years of age. There were no new or unexpected safety issues following vaccination in females 9 years of age.
Studies in Females 26 Years of Age and Older: In one large controlled study, 5752 women aged 26 years and older received at least one dose of CERVARIX or one dose of $Al(OH)_3$ control. There were no clinically meaningful differences in overall safety outcomes between treatment groups. In addition, there were no new or unexpected safety issues in women 26 years and older compared to women 15-25 years of age.
Less Common Clinical Trial Adverse Drug Reactions (<1%): Blood and Lymphatic System Disorders: Uncommon: lymphadenopathy.
General Disorders and Administration Site Conditions: Uncommon: other injection site reactions such as induration and local paresthesia.
Post-Market 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 (≥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 (≥1/10 000 to <1/1000).

DRUG INTERACTIONS: Drug-Drug Interactions: Use with Other Vaccines: CERVARIX may be administered concomitantly with BOOSTRIX-POLIO (combined diphtheria, tetanus, pertussis [acellular] and inactivated poliomyelitis vaccine), BOOSTRIX (combined diphtheria, tetanus and pertussis [acellular] vaccine) or MENACTRA (meningococcal groups A, C, Y and W-135 polysaccharide diphtheria toxoid conjugate vaccine), without clinically relevant interference with antibody response to any of the components of either vaccine.

NOTE: HPV-16 and HPV-18 Antibodies: Although the criteria for non-inferiority were met for secondary immunogenicity endpoints with respect to anti-HPV-16 and anti-HPV-18 seroconversion rates and GMTs evaluated one month post Dose 3, the GMTs are observed to be consistently lower for all the co-administration groups.

Pertussis Antibodies: Although the criteria for non-inferiority were met for the secondary immunogenicity endpoints anti-PT, anti-PRN and anti-FHA GMTs, evaluated one month post Dose 1 (Month 1) for HPV+B+M¶ compared to B/HPV†, the GMTs were lower for the three antibodies for the co-administration group and statistically lower for anti-FHA.

Meningococcal Antibodies: Although the criteria for non-inferiority were met for the secondary immunogenicity endpoints with respect to the percentage of subjects with meningococcal anti-A, anti-C, anti-Y and anti-W-135 GMTs one month post-vaccination for HPV+B+M¶ compared to M/HPV‡, the GMTs were lower for the four antibodies for the co-administration group and **statistically significantly lower for anti-A and anti-W-135**.

CERVARIX may be administered concomitantly with the combined hepatitis A and hepatitis B vaccine (TWINRIX Junior) or the 10 µg/0.5 mL dose of ENGERIX-B (hepatitis B recombinant vaccine). Administration of CERVARIX at the same time as TWINRIX Junior or the 10 µg/0.5 mL dose of ENGERIX-B has shown no clinically relevant interference in the antibody response to the HPV16/18 antigens in CERVARIX and the hepatitis A antigen in TWINRIX Junior. Anti-hepatitis B geometric mean antibody titers were lower on co-administration of the vaccines but the percentage of subjects reaching anti-HBs ≥10 mIU/mL (seroprotection) was 98.3% for concomitant vaccination with TWINRIX Junior and 97.8% with ENGERIX-B, and 100% for TWINRIX Junior and ENGERIX-B given alone. The clinical relevance of the reduced antibody titre and the risk of a substantially reduced immune response to hepatitis B if doses of hepatitis B vaccine are missed are not known.

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 Test 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.

¶ HPV+B+M=BOOSTRIX vaccine administered at Month 0. MENACTRA vaccine administered at Month 0. CERVARIX vaccine administered at Month 0, 1 and 6.
† B/HPV=BOOSTRIX vaccine administered at Month 0. CERVARIX vaccine administered at Month 1, 2 and 7.
‡ M/HPV=MENACTRA vaccine administered at Month 0. CERVARIX vaccine administered at Month 1, 2 and 7.

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DOSAGE AND ADMINISTRATION: Recommended Dose and Dosage Adjustment: The vaccination schedule depends on the age of the individual.

From age 9 to and including 14 years of age at the time of the first injection, CERVARIX can be administered as either a 2 or 3 dose schedule. Limited data are available at present on long term antibody persistence for the 2 dose schedule.

From 15 to 45 years of age, only the 3-dose schedule is recommended.

- **2-dose schedule:** the vaccination schedule is 0, 6 months. If flexibility in the vaccination schedule is necessary, the second dose can be administered between 5 and 7 months after the first dose.
- **3-dose schedule:** The 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 12 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.

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.

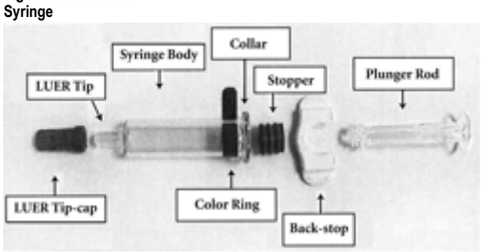
A fine white deposit with a clear, colourless supernatant may be observed upon storage of the syringe/vial. This does not constitute a sign of deterioration.

Shake well before use. After shaking, CERVARIX is a white cloudy liquid.

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. See Figure 1.

Figure 1: CERVARIX Syringe



OVERDOSAGE:

For management of a suspected drug overdose, contact your regional Poison Control Centre. See the *CPS* Directory section for a list of Poison Control Centres.

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 Pap$ smear, with progression in degree of dysplasia.

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 7/100 000 and the annual mortality rate is 2/100 000. 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 1350 new cases and 390 deaths from cervical cancer estimated in 2012. The annual economic burden of HPV-related disease is estimated to be close to $300 million. The majority of the burden represents the cost of the more than 3.9 million Pap tests that produce negative or false-positive results followed by, in decreasing order, the cost of cervical intraepithelial neoplasia (CIN) grades 1/2/3, the cost of cervical cancer, and the cost of genital warts.

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 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.

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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.

Evidence of Anamnestic (Immune Memory) Response: Based on a subset of subjects from the original study HPV-001, the administration of a challenge dose after a mean of 6.8 years following the first vaccination elicited an anamnestic immune response to HPV-16 and HPV-18 (by ELISA and pseudovirion-based neutralizing assay) at day 7. One month after the challenge dose, geometric mean titers (GMTs) exceeded those observed one month after the primary vaccination course. An anamnestic response was also observed for the related types HPV-31 and HPV-45 by ELISA. All subjects were seropositive for anti-HPV-16 and anti-HPV-18 prior to the challenge dose. GMT ratios are presented in Table 5.

Table 5: CERVARIX
GMT Ratios and 95% CI at Day 7 and One Month After the Administration of a Challenge Dose (ATP Cohort)

N	Time Point 1	GMT1	Time Point 2	GMT2	Ratio GMT1/ GMT2	LL	UL
HPV-16							
59	Day 7	6246.7	PRE	720.7	8.7	6.3	11.9
40[a]	1 month post 4th dose	15402.8	1 month post 3rd dose	6298.6	2.4	1.7	3.5
HPV-18							
59	Day 7	4126.7	PRE	502.9	8.2	6.1	11.1
40[a]	1 month post 4th dose	8259.3	1 month post 3rd dose	5350.9	1.5	1.1	2.1
HPV-31							
59	Day 7	2154.8	PRE	222.4	9.7	7.5	12.5
HPV-45							
59	Day 7	2456.7	PRE	202.7	12.1	9.4	15.6

[a] Subjects included in the ATP cohort of HPV-001 and included in the ATP cohort of the challenge dose study (HPV-024).
Legend: GMTs measured by ELISA.
N=number of subjects with results available at both time-points; PRE=pre-vaccination of the challenge dose; LL/UL=lower/upper limit of the 95% confidence interval.
The ATP cohort included all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures were available. This included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination.

§ Pap (Papanicolaou test detects abnormal cervical cells).

STORAGE AND STABILITY: Store in a refrigerator at 2 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 and 25°C or up to one day at temperatures between 25 and 37°C. If exposed to temperatures >37°C, discard vaccine.

DOSAGE FORMS, COMPOSITION AND PACKAGING: Each 0.5 mL dose of suspension for injection contains: Human Papillomavirus type 16 L1 protein¶ 20 µg and Human Papillomavirus type 18 L1 protein¶ 20 µg. Nonmedicinal ingredients: aluminum hydroxide, hydrated ($Al(OH)_3$) **, sodium chloride, sodium dihydrogen phosphate dihydrate, 3-0-desacyl-4'-monophosphoryl lipid A (MPL)** and water for injection. Pre-filled syringes (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 (type I glass) with a stopper (rubber butyl) in pack sizes of 1, 10 and 100.

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

** The GlaxoSmithKline proprietary AS04 adjuvant system is composed of aluminum hydroxide and 3-0-desacyl-4'-monophosphoryl lipid A (MPL).

INFORMATION FOR THE PATIENT: Published online and available by subscription at www.pharmacists.ca/cps and www.pharmacists.ca/rxtx

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