Cervarix™

1. Name of the medicinal product

Cervarix™

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

2. Qualitative and quantitative composition

1 dose (0.5 ml) contains:

Human Papillomavirus type 16 L1 protein[1]	20 micrograms
Human Papillomavirus type 18 L1 protein[1]	20 micrograms
3-*O*-desacyl-4'- monophosphoryl lipid A (MPL)[2]	50 micrograms
Aluminium hydroxide, hydrated[2]	0.5 milligrams Al^{3+}

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

[2]The GlaxoSmithKline proprietary AS04 adjuvant system is composed of aluminium hydroxide and 3-*O*-desacyl-4'- monophosphoryl lipid A (MPL) (see section 5.1)

3. Pharmaceutical form

Suspension for injection.

4. Clinical particulars

4.1 Therapeutic indications

Cervarix™ is indicated for the prevention of cervical cancer (squamous-cell carcinoma and adenocarcinoma) by protecting against incident and persistent infections, cytological abnormalities including atypical squamous cells of undetermined significance (ASC-US) and cervical intraepithelial neoplasia (CIN), CIN1 and pre-cancerous lesions (CIN2 and CIN3) caused by oncogenic Human Papillomavirus (HPV) Types 16 and 18.

The indication is based on the demonstration of efficacy in women aged 15 – 25 years following vaccination with *Cervarix*™ and on the immunogenicity of vaccine in girls and women aged 10 – 25 years.

The use of *Cervarix*™ should be in accordance with official recommendations.

4.2 Posology and method of administration

The primary vaccination course consists of three doses.

The recommended vaccination schedule is 0, 1, 6 months. If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose. The necessity for a booster dose has not been established (see section 5.1).

Cervarix™ is for intramuscular injection in the deltoid region (see sections 4.4 and 4.5).

4.3 Contra-indications

Cervarix™ should not be administered to subjects with known hypersensitivity to any component of the vaccine (see sections 2 and 6.1).

4.4 Special warnings and special precautions for use

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

As with other vaccines, the administration of *Cervarix™* should be postponed in subjects suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

Cervarix™ should under no circumstances be administered intravascularly or intradermally. No data are available on subcutaneous administration of *Cervarix™*.

As for other vaccines administered intramuscularly, *Cervarix™* should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

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

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

HPV-16 and HPV-18 are not responsible for all cervical cancers (see section 5.1). Other oncogenic HPV types can also cause cervical cancer. HPV infections and related clinical outcomes due to these other oncogenic types may not be prevented by vaccination.

Vaccination is primary prevention and is not a substitute for regular cervical screening (secondary prevention) or for precautions against exposure to HPV and sexually transmitted diseases. Vaccination alongside cervical screening will reduce the risk of cervical cancer further than screening alone. It is important to continue cervical screening (i.e. pap smear, VIA) after vaccination and follow recommended local screening guidelines.

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

Duration of protection has not been established. Sustained protective efficacy has been observed for at least 5.5 years after the first dose. Long-term studies are ongoing to establish the duration of protection (see section 5.1).

4.5 Interaction with other medicaments and other forms of interaction

Use with other vaccines

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.

Use with hormonal contraceptive

In clinical efficacy studies, approximately 60% of women who received *Cervarix™* used hormonal contraceptives. There is no evidence that the use of hormonal contraceptives has an impact on the efficacy of *Cervarix™*.

Use with systemic immunosuppressive medications

As with other vaccines it may be expected that in patients receiving immunosuppressive treatment an adequate response may not be elicited.

4.6 Use during pregnancy and lactation

Pregnancy

Specific studies of the vaccine in pregnant women were not conducted. During the prelicensure clinical development program, pregnancies have been reported. These data are insufficient to recommend use of *Cervarix*™ during pregnancy. Vaccination should, therefore, be postponed until after completion of pregnancy.

The effect of *Cervarix*™ on embryo-foetal, 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/foetal development, parturition or post-natal development.

Lactation

The effect on breast-fed 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-HPV16 and anti-HPV18 antibodies via the milk during the lactation period in rats. However, it is unknown whether vaccine-induced antibodies are excreted in human breast milk.

4.7 Effect on ability to drive and use machines

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

4.8 Undesirable effects

In clinical studies, a total of approximately 45,000 doses of *Cervarix*™ were administered to approximately 16,000 subjects aged 10-68 years. These subjects were followed to assess the safety of the vaccine.

The most common reaction observed after vaccine administration was injection site pain which occurred after 78% of all doses. The majority of these reactions were of mild to moderate severity and were not long lasting.

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

Frequencies are reported as:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Infections and infestations:

Uncommon: upper respiratory tract infection

Nervous system disorders:

Very common: headache

Uncommon: dizziness

Gastrointestinal disorders:

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

Skin and subcutaneous tissue disorders:
Common: itching/pruritus, rash, urticaria

Musculoskeletal and connective tissue and bone disorders:
Very common: myalgia
Common: arthralgia

General disorders and administration site conditions:
Very common: injection site reactions including pain, redness, swelling; fatigue
Common: fever (≥38°C)
Uncommon: other injection site reactions such as induration, local paraesthesia

4.9 Overdose
Insufficient data are available

5. Pharmacological particulars

5.1. Pharmacodynamic properties.
Mechanism of Action
Persistent infection with oncogenic HPV types has been demonstrated to be responsible for virtually all cases of cervical cancer worldwide.
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. Animal studies have shown that the efficacy of L1 VLP vaccines is largely mediated by the development of an humoral immune response and cell-mediated immune memory.

Cervarix™ is adjuvanted with AS04 which has been shown in clinical trials to induce a higher and long lasting immune response compared to the same antigens adjuvanted with aluminium salt [Al(OH)3] alone.

Based on a large consensus among experts ("HPV vaccines and screening in the prevention of Cervical Cancer", Vaccine 24, supplement 3, 31 Aug 2006), the most common HPV types identified in cervical cancer were, in decreasing order of frequency, HPV-16, -18, -45, -31, -33, -52, -58, -35, -59, -56, -39, -51, -73, -68 and -66.
The prevalence rates of HPV-16 and HPV-18 related clinical outcomes are presented in the table below:

	Overall	Central South America	Asia	Africa
Invasive cervical cancer	65-77%	65%	67%	72%
CIN2/3 (*)	41-57%	48%	41%	48%
CIN1 (**)	15-32%	21%	32%	15%
ASC-US (***)	8-19%	8%	NA	NA

(*) corresponding to HSIL (high grade squamous intraepithelial lesions)
(**) corresponding to LSIL (low grade squamous intraepithelial lesions)
(***) atypical squamous cells of undetermined significance
NA: not available

Prophylactic Efficacy

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

Clinical trial HPV-001/007 was conducted in North America and Latin America. Study entry criteria were: negative for oncogenic HPV DNA (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) in cervical samples, seronegative for HPV-16 and HPV-18 antibodies and normal cytology. These characteristics are representative of a population unlikely to have been exposed to oncogenic HPV types prior to vaccination ("unexposed population").

Clinical trial HPV-008 was conducted in North America, Latin America, Europe, Asia Pacific and Australia. Pre-vaccination samples were collected for oncogenic HPV DNA (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) testing and serum testing for HPV-16 and HPV-18 antibodies. Women were vaccinated regardless of baseline cytology and HPV status. These characteristics are representative of a "general population" including women exposed to HPV infection prior to vaccination.

As in any prophylactic efficacy trial, subjects initially infected with a particular HPV type were not eligible for the efficacy assessment of that type.

In both studies the following endpoints were evaluated:

- CIN2+ (cervical intraepithelial neoplasia grade 2 and higher grade lesions)
- CIN1+ (cervical intraepithelial neoplasia grade 1 and higher grade lesions)
- cytological abnormalities including atypical squamous cells of undetermined significance (ASC-US), low grade squamous intraepithelial lesions (LSIL), high grade squamous intraepithelial lesions (HSIL) and ASC-US of suspected high grade (ASC-H).
- 12 month persistent infection (i.e. at least 2 positive specimens for the same HPV type over approximately a 12-month interval but no negative sample in between)
- 6 month persistent infection (i.e. at least 2 positive specimens for the same HPV type over approximately a 6-month interval but no negative sample in between)

Efficacy against HPV-16/18 in the "unexposed population" to oncogenic HPV types

Efficacy results in the "unexposed population" for histological endpoints in study HPV-001/007 (Total Cohort i.e. women who received at least one vaccine dose) are presented in the table below.

Endpoint	*Cervarix*™ N = 481	Control (Aluminium salt) N = 470	% Efficacy (95% CI)
	Number of cases		
CIN2+	0	7	100% (CI: 32.7;100)
CIN1+	0	11	100% (CI: 61.5;100)

Efficacy against HPV-16/18 cytological abnormalities was 96.4% (CI: 86.3;99.6).

Efficacy against HPV-16/18 persistent infection was 97.9% (CI: 87.8;99.9) and 95.9% (CI: 74.7;99.9) by a 6-month and a 12-month definition, respectively.

In study HPV-001/007, women were followed for efficacy for at least 64 months after dose one. Despite evidence of continuous exposure to HPV infections as observed in the control group, there is no evidence of waning protection in vaccinated women.

Efficacy against HPV-16/18 in the "general population" including women with current or prior oncogenic HPV infection

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

Efficacy results in the "general population" for histological endpoints in study HPV-008 (Total Vaccinated Cohort i.e. women who received at least one vaccine dose) are presented in the table below.

Endpoint	*Cervarix*™ N = 7788	Control (Hepatitis A vaccine) N = 7838	% Efficacy (95% CI)
	Number of cases		
CIN2+	0*	20*	100% (CI: 74.2;100)
CIN1+	1*	26*	96.1% (CI: 71.6;100)

* In 1 additional case of CIN1 (in the control group) and 3 additional cases of CIN2+ (2 in the *Cervarix*™ group and 1 in the control group), an oncogenic HPV type was found in the lesion simultaneously with HPV-16 or HPV-18. Based on a case allocation considering that the HPV type causing the lesion must be detected both in the lesion and in at least one of the two immediately preceding cervical samples, these four cases were excluded from the analysis of vaccine efficacy.

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

Efficacy against HPV-16/18 cytological abnormalities was 82.2% (CI: 72.0;89.2). In 51% of the ASC-US cases, the onset of infection was before completion of the vaccination course. Efficacy against HPV-16/18 persistent infection was 75.9% (CI: 47.7;90.2) by a 12-month definition. In 93% of the cases the onset of infection was before completion of the full vaccination course.

Efficacy against infection by oncogenic HPV types other than HPV-16 and HPV-18

HPV-16 and HPV-18 are not responsible for all cervical cancers. Other oncogenic HPV types can also cause cervical cancer. Of these, HPV-45 and HPV-31 are the next most prevalent worldwide.

In the "unexposed population" (study HPV-001/007), vaccine efficacy against incident infection was 53.5% (CI: 14.8;75.6) for HPV type 31 and 88% (CI: 60.5;97.7) for HPV type 45. In the "general population" (study HPV-008), vaccine efficacy against persistent infection (6-month definition) was 36.1% (CI: 0.5;59.5) for HPV type 31, 59.9% (CI: 2.6;85.2) for HPV type 45. In the majority of these cases the onset of infection was before completion of the vaccination course (vaccine or control).

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

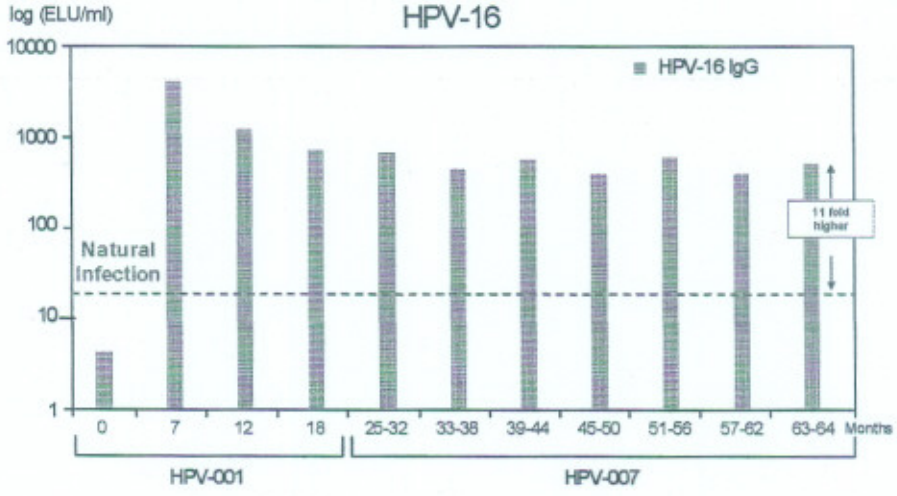
Vaccine-Induced Immunogenicity

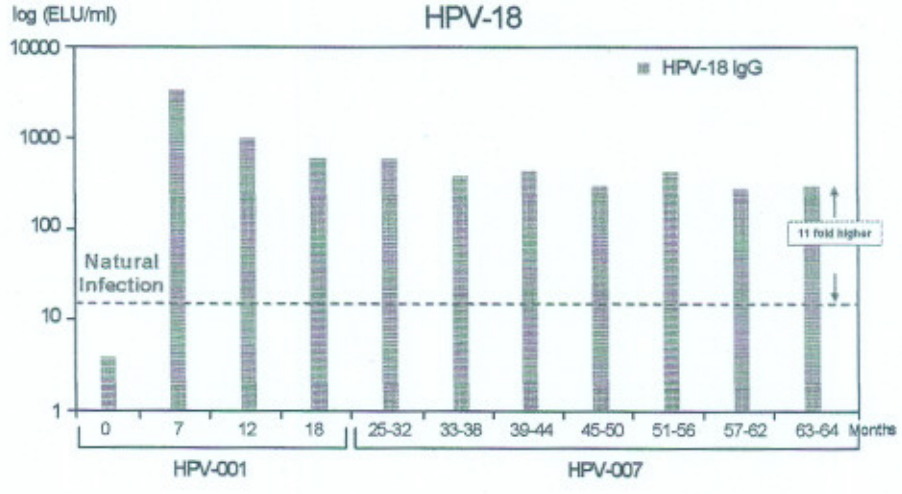
The antibody response to HPV-16 and HPV-18 was measured using a type specific ELISA which was shown to strongly correlate with neutralisation assays (including pseudovirion based assay developed by the US National Cancer Institute). Transudation of antibodies from serum to the cervical mucosa has been demonstrated in clinical trials.

The immunogenicity induced by three doses of *Cervarix™* has been evaluated in 5,303 female subjects from 10 to 55 years of age. In clinical trials, 99.9% of initially seronegative subjects had seroconverted to both HPV type 16 and 18 one month after the third dose. Vaccine-induced IgG Geometric Mean Titres (GMT) were well above titres observed in women previously infected but who cleared HPV infection (natural infection). Initially seropositive and seronegative subjects reached similar titres after vaccination.

Immunogenicity in women aged 15 to 25 years

The immune response against HPV-16 and HPV-18 was evaluated up to 64 months post dose one, in study HPV-001/007 in women 15 to 25 years old at the time of vaccination. Results are presented in the graphs below:





Vaccine-induced IgG Geometric Mean Titres (GMT) for both HPV-16 and HPV-18 peaked at month 7 and then declined to reach a plateau from month 18 up to the end of the follow-up (month 64). At the end of the follow-up period, GMTs for both HPV-16 and HPV-18 were

still at least 11-fold higher than titres observed in women previously infected but who cleared HPV infection (natural infection). In study HPV-008 ("general population"), immunogenicity at month 7 was similar to the response observed in study HPV-001/007 ("unexposed population").
In another clinical trial (study 014) performed in women aged 15 to 55 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7). The GMTs were, however, lower in women above 25 years. Nevertheless, all subjects remained seropositive for both types throughout the follow-up phase (up to month 18) maintaining antibody levels at an order of magnitude above those encountered after natural infection.

Bridging the efficacy of Cervarix™ demonstrated in 15 to 25 year olds to other age groups
In two clinical trials performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV type 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher as compared to women aged 15 to 25 years. On the basis of these immunogenicity data, the efficacy of *Cervarix™* in inferred from 10 to 14 years of age.

5.2 Pharmacokinetic properties
Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, fertility, embryo-foetal and postnatal toxicity (up to the end of the lactation period).

6. Pharmaceutical particulars
6.1 List of excipients
Sodium chloride, sodium dihydrogen phosphate dihydrate, water for injections

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
The expiry date of the vaccine is indicated on the label and packaging.

6.4 Special precautions for storage
Store in a refrigerator (+2°C to +8°C). Do not freeze.
Store in the original package in order to protect from light.
In case of temporary storage of the vaccine outside refrigerator, experimental data have shown that the vaccine is stable when stored at temperatures up to 37°C for 1 week. These data are not recommendations for storage.

6.5 Nature and contents of container
0.5 ml of suspension in a pre-filled syringe (type I glass) with a plunger stopper (rubber butyl) with or without needles.
0.5 ml of suspension in vial (type I glass) with a stopper (rubber butyl).
Cervarix™ is presented as a turbid white suspension. Upon storage, a fine white deposit with a clear colourless supernatant can be observed.

6.6 Instructions for use, handling and disposal

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. The vaccine should be well shaken before use. Any unused product or waste material should be disposed of in accordance with local requirements.

Cervarix is a trademark.

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Presentations

Box, Prefilled Syringe of 0.5 ml	Reg. No. xxxxxxxxxxxxxx
Box, Vial of 0.5 ml	Reg. No. xxxxxxxxxxxxxx

HARUS DENGAN RESEP DOKTER

Imported by
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Bogor, Indonesia

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