This file displays the English text version of the leaflet approved for supply of the vaccine through UN agencies. An image of the updated multilingual PI as laid out for supply with the vaccines will be published when available.

Also, in order to reduce leaflet volume, WHO agreed that the section 5. PHARMACOLOGICAL PROPERTIES could be omitted from the leaflet, provided that full details were available on this site.

# WHO PRODUCT INFORMATION

## 1. NAME OF THE MEDICINAL PRODUCT

**Cervarix**, suspension for injection
Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

| | |
|---|---|
| Human Papillomavirus[1] type 16 L1 protein[2,3,4] | 20 micrograms |
| Human Papillomavirus[1] type 18 L1 protein[2,3,4] | 20 micrograms |

[1]Human Papillomavirus = HPV

[2]adjuvanted by AS04 containing:

| | |
|---|---|
| 3-*O*-desacyl-4'- monophosphoryl lipid A (MPL)[3] | 50 micrograms |
| [3]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$) | 0.5 milligrams $Al^{3+}$ in total |

[4]L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system which uses Hi-5 Rix4446 cells derived from *Trichoplusia ni*.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Suspension for injection.
Turbid white suspension.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**Cervarix** is a vaccine for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic Human Papillomavirus (HPV) types. See sections 4.4 and 5.1 for important information on the data that support this indication.

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

### 4.2 Posology and method of administration

Posology

The vaccination schedule depends on the age of the subject.

| Age at the time of the first injection | Immunization and schedule |
|---|---|
| 9 to and including 14 years* | Two doses each of 0.5 ml.<br>The second dose given between 5 and 13 months after the first dose |
| From 15 years and above | Three doses each of 0.5 ml at 0, 1, 6 months** |

*If the second vaccine dose is administered before the 5th month after the first dose, a third dose should always be administered.
**If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose.

The need for a booster dose has not been established (see section 5.1).

It is recommended that subjects who receive a first dose of **Cervarix** complete the vaccination course with **Cervarix** (see section 4.4).

*Paediatric population (children < 9 years of age)*

**Cervarix** is not recommended for use in children below 9 years of age due to lack of data on safety and immunogenicity in this age-group.

Method of administration

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

**Cervarix** should under no circumstances be administered intravascularly or intradermally. No data are available on subcutaneous administration of **Cervarix** (see section 4.4).

If **Cervarix** is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites (see section 4.5).

### 4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

### 4.4 Special warnings and precautions for use

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

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

Administration of **Cervarix** should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a cold, is not a contraindication for immunization.

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

As with 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** will only protect against diseases that are caused by HPV types 16 and 18 and to some extent against diseases caused by certain other oncogenic related HPV types (see section 5.1). Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.

The vaccine is for prophylactic use only and has no effect on active HPV infections or established clinical disease. The vaccine has not been shown to have a therapeutic effect. The vaccine is therefore not indicated for treatment of cervical cancer or cervical intraepithelial neoplasia (CIN). It is also not intended to prevent progression of other established HPV-related lesions or existing HPV infections with vaccine or non-vaccine types (see section 5.1 "Efficacy in women with evidence of HPV-16 or HPV-18 infection at study entry.").

Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100% effective and **Cervarix** will not provide protection against every HPV type, or against existing HPV infections, routine cervical screening remains critically important and should follow local recommendations.

Duration of protection has not fully been established. Timing and need of booster dose(s) has not been established.

Except for asymptomatic human immunodeficiency virus (HIV) infected subjects for whom limited immunogenicity data are available (see section 5.1), there are no data on the use of **Cervarix** in subjects with impaired immune responsiveness such as patients receiving immunosuppressive treatment. As with other vaccines, an adequate immune response may not be elicited in these individuals.

There are no safety, immunogenicity or efficacy data to support interchangeability of **Cervarix** with other HPV vaccines.

## 4.5 Interaction with other medicinal products and other forms of interaction

In all clinical trials individuals who had received immunoglobulin or blood-derived products within 3 months prior to the first vaccine dose were excluded.

*Use with other vaccines*

**Cervarix** may be administered concomitantly with:
- a combined booster vaccine containing diphtheria (d), tetanus (T) and pertussis [acellular] (pa) with or without inactivated poliomyelitis (IPV), (dTpa, dTpa-IPV vaccines),

- a combined hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (HAB vaccine).

If **Cervarix** is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

*Use with hormonal contraceptive*

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

*Use with systemic immunosuppressive medicinal products*

See section 4.4.

## 4.6 Pregnancy and lactation

Pregnancy

Specific studies of the vaccine in pregnant women were not conducted. Data in pregnant women collected as part of pregnancy registries, epidemiological studies and inadvertent exposure during clinical trials are insufficient to conclude whether or not vaccination with **Cervarix** affects the risk of adverse pregnancy outcomes including spontaneous abortion.
However, during the clinical development program, a total of 10,476 pregnancies were reported including 5,387 in women who had received **Cervarix**. Overall, the proportions of pregnant subjects who experienced specific outcomes (e.g., normal infant, abnormal infants including congenital anomalies, premature birth, and spontaneous abortion) were similar between treatment groups.

Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of **Cervarix**during pregnancy. Women who are pregnant or trying to become pregnant, are advised to postpone or interrupt vaccination until completion of pregnancy.

Breast-feeding

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.

Fertility

No fertility data are available.

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. However, some of the effects mentioned under section 4.8 “Undesirable effects” may temporarily affect the ability to drive or use machines.

## 4.8 Undesirable effects

**Summary of safety profile**
In clinical studies that enrolled girls and women aged from 10 up to 72 years (of which 79.2% were aged 10-25 years at the time of enrolment), **Cervarix** was administered to 16,142 females whilst 13,811 females received control. These subjects were followed for serious adverse events over the entire study period. In a pre-defined subset of subjects (**Cervarix** = 8,130 versus control = 5,786), adverse events were followed for 30 days after each injection. In two clinical studies that enrolled males aged 10 to 18 years, 2,617 males received **Cervarix** and were followed-up with active safety surveillance.

The most common adverse 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.

**Tabulated list of adverse reactions**
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)

| System Organ Class | Frequency | Adverse reactions |
|---|---|---|
| **Clinical trials** | | |
| Infections and infestations | Uncommon | Upper respiratory tract infection |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness |
| Gastrointestinal disorders | Common | Gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain |
| Skin and subcutaneous tissue disorders | Common | Itching/pruritus, rash, urticaria |
| Musculoskeletal and connective tissue 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 |
| **Post-marketing experience** | | |
| Blood and lymphatic system disorders | Not known* | Lymphadenopathy |
| Immune system disorders | Not known* | Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema |
| Nervous system disorders | Not known* | Syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements (see section 4.4) |

*Because these events were reported spontaneously, it is not possible to reliably estimate their frequency

In clinical trials a similar safety profile has been observed in subjects with prior or current HPV infection as compared to subjects negative for oncogenic HPV DNA or seronegative for HPV-16 and HPV-18 antibodies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

### 4.9 Overdose

No case of overdose has been reported.

## 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

*Clinical studies*

Clinical efficacy in women aged 15 to 25 years

The efficacy of **Cervarix** was assessed in two controlled, double-blind, randomised Phase II and III clinical trials that included a total of 19,778 women aged 15 to 25 years.

**1. Phase II study (study HPV-001/007)**
The primary efficacy endpoint was incident infection with HPV-16 and/or HPV-18. Twelve-month persistent infection was evaluated as additional efficacy endpoint.

Prophylactic efficacy against HPV-16/18 infection in a population naïve to oncogenic HPV types

Women (N=1,113) were vaccinated in study 001 and evaluated for efficacy up to month 27. A subset of women (N=776) vaccinated in study 001 was followed in study 007 up to 6.4 years (approximately 77 months) after the first dose (mean follow-up of 5.9 years). In study 007 the efficacy of **Cervarix** against 12-month persistent HPV-16/18 infection was 100% (95% CI: 80.5; 100).

In study HPV-023, subjects from the Brazilian cohort (N=437) of study 001/007 were followed up to a mean of 8.9 years (standard deviation 0.4 years) after the first dose. At study completion, there were no cases of infection or histopathological lesions associated with HPV-16 or HPV-18 in the vaccine group in study HPV-023. In the placebo group, there were 4 cases of 6-month persistent infection and 1 case of 12-month persistent infection. The study was not powered to demonstrate a difference between the vaccine and the placebo group for these endpoints.

**2. Phase III study (study HPV-008)**
The primary efficacy endpoint was CIN2+ associated with HPV-16 and/or HPV-18 (HPV-16/18). Cervical Intraepithelial Neoplasia (CIN) grade 2 and 3 (CIN2/3) and cervical adenocarcinoma in situ (AIS) were used in the clinical trials as surrogate markers for cervical cancer.
The secondary endpoints included 6- and 12-month persistent infection.
Persistent infection that lasts for at least 6 months has also been shown to be a relevant surrogate marker for cervical cancer.

2.1 Prophylactic efficacy against HPV-16/18 in women naïve to HPV-16 and/or HPV-18
In study HPV-008, the primary analyses of efficacy were performed on the According to Protocol cohort (ATP cohort: including women who received 3 vaccine doses and were DNA negative and seronegative at month 0 and DNA negative at month 6 for the HPV type considered in the analysis). Overall, 74% of women enrolled were naïve to both HPV-16 and HPV-18 (i.e. DNA negative and seronegative at study entry).
Two analyses of study HPV-008 have been performed: an event-triggered analysis performed once at least 36 CIN2+ cases associated with HPV-16/18 were accrued in the ATP cohort and an end-of study analysis.
Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 observed in the ATP cohort at the end of study is presented in Table 1.

***Table 1: Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 (ATP cohort)***

| **HPV-16/18 endpoint** | **ATP cohort[1]** | | |
|---|---|---|---|
| | **End of study analysis[3]** | | |
| | **Cervarix (N = 7338)** | **Control (N = 7305)** | **% Efficacy (95% CI)** |
| | **n[2]** | **n** | |
| **CIN2+** | 5 | 97 | 94.9% (87.7;98.4) |
| **CIN3+** | 2 | 24 | 91.7% (66.6;99.1) |
| N = number of subjects included in each group<br>n = number of cases | | | |

(1) ATP: includes women who received 3 doses of vaccine, were DNA negative and seronegative at month 0 and DNA negative at month 6 to the relevant HPV type (HPV-16 or HPV-18)
(2) including 4 cases of CIN2+ and 2 cases of CIN3+ in which another oncogenic HPV type was identified in the lesion, concomitantly with HPV-16 or HPV-18. These cases are excluded in the HPV type assignment analysis (see under Table).
(3) mean follow-up of 40 months post dose 3

At the event-triggered analysis the efficacy was 92.9% (96.1% CI:79.9;98.3) against CIN2+ and 80% (96.1% CI: 0.3;98.1) against CIN3+. In addition, statistically significant vaccine efficacy against CIN2+ associated with HPV-16 and HPV-18 individually was demonstrated.

At end of study analysis, there were 2 cases of VIN2+ or VaIN2+ associated with HPV-16 or HPV-18 in the vaccine group and 7 cases in the control group in the ATP cohort. The study was not powered to demonstrate a difference between the vaccine and the control group for these endpoints.

Vaccine efficacy was demonstrated against virological endpoints associated with HPV-16/18 in the ATP cohort at the end of study:

- 6 month persistent infection: 94.3% (95% CI: 92;96.1)
- 12 month persistent infection: 92.9% (95% CI: 89.4;95.4 )

The efficacy results at the event-triggered analysis were 94.3% (96.1% CI: 91.5;96.3) against 6-month persistent infection and 91.4% (96.1% CI: 89.4;95.4) against 12-month persistent infection.

2.2 Efficacy against HPV-16/18 in women with evidence of HPV-16 or HPV-18 infection at study entry.

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

2.3 Efficacy against HPV types 16 and 18 in women with and without prior infection or disease.

The Total Vaccinated Cohort (TVC) included all subjects who received at least one dose of the vaccine, irrespective of their HPV DNA status, cytology and serostatus at baseline. This cohort included women with or without current and/or prior HPV infection.

Vaccine efficacy against high grade cervical lesions and virological endpoints (persistent infection) associated with HPV-16/18 observed in TVC at the end of study was as follows:
- CIN2+: 60.7% (95% CI: 49.6;69.5)
- CIN3+: 45.7% (95% CI: 22.9;62.2)
- 6-month persistent infection: 60.9% (95% CI: 56.6;64.8)
- 12-month persistent infection: 57.5% (95% CI: 51.7;62.8)

2.4 Overall impact of the vaccine on cervical HPV disease burden

In study HPV-008, the incidence of high grade cervical lesions was compared between the placebo and vaccine group irrespective of the HPV DNA type in the lesion. In the TVC and TVC-naïve cohorts, the vaccine efficacy was demonstrated against high-grade cervical lesions at the end of study. The TVC-naïve is a subset of the TVC that includes women with normal cytology, and who were HPV DNA negative for 14 oncogenic HPV types and seronegative for HPV-16 and HPV-18 at baseline.

Vaccine efficacy against high grade cervical lesions irrespective of the HPV DNA-type in the lesion observed at the end of study in TVC-naïve and TVC was as follows:
- CIN2+: 64.9% (95% CI: 52.7;74.2) in TVC-naïve and 33.1% (95% CI: 22.2;42.6) in TVC.
- CIN3+: 93.2% (95% CI: 78.9;98.7) in TVC-naïve and 45.6% (95% CI:28.8;58.7) in TVC.

At the end of study analysis, **Cervarix** reduced definitive cervical therapy procedures (includes loop electrosurgical excision procedure [LEEP], cold-knife Cone, and laser procedures) by 70.2% (95% CI: 57.8;79.3) in TVC-naïve and 33.2% (95% CI: 20.8;43.7) in TVC.

2.5 Cross-protective efficacy

The cross-protective efficacy of **Cervarix** against histopathological and virological endpoints (persistent infection) has been evaluated in study HPV-008 for 12 non-vaccine oncogenic HPV types. The study was not powered to assess efficacy against disease caused by individual HPV types. HPV-31, 33 and 45 showed consistent cross-protection for 6-month persistent infection and CIN2+ endpoints in all study cohorts.

Clinical efficacy in women aged 26 years and older

The efficacy of **Cervarix** was assessed in a double-blind, randomised Phase III clinical trial (HPV-015) that included a total of 5777 women aged 26 years and older. The study was conducted in North America, Latin America, Asia Pacific and Europe, and allowed women with previous history of HPV disease/infection to be enrolled. An interim analysis was performed when all subjects had completed the month 48 study visit.
The primary analyses of efficacy were performed on the ATP cohort for efficacy and the TVC.

Vaccine efficacy against 6 month persistent infection with HPV-16/18 (relevant surrogate marker for cervical cancer) is summarised in the following table.

***Table 7: Vaccine efficacy against 6M PI with HPV 16/18 in ATP and TVC***

| HPV-16/18 endpoint | ATP[1] | | | TVC[2] | | |
|---|---|---|---|---|---|---|
| | Cervarix n/N | Control n/N | % Efficacy (97.7% CI) | Cervarix n/N | Control n/N | % Efficacy (97.7% CI) |
| 6M PI | 6/1859 | 34/1822 | 82.9% (53.8; 95.1) | 71/2767 | 132/2776 | 47% (25.4; 62.7) |

N= number of subject in each group
n= number of subjects reporting at least one event in each group
6M PI = 6-month persistent infection
CI = Confidence Interval
(1) 3 doses of vaccine, DNA negative and seronegative at month 0 and DNA negative at month 6 for the relevant HPV type (HPV-16 and/or HPV-18)
(2) at least one dose of vaccine, irrespective of HPV DNA and serostatus at month 0. Includes 15% of subjects with previous history of HPV disease/infection

Vaccine efficacy against 6-month persistent infection was 79.1% (97.7% CI [27.6; 95.9]) for HPV-31 and 76.9% (97.7% CI [18.5; 95.6]) for HPV-45 in the ATP cohort (3 doses of vaccine, DNA negative at months 0 and 6 for the relevant HPV type).

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

*Immunogenicity*

The immunogenicity induced by three doses of **Cervarix** has been evaluated in 5,465 female subjects from 9 to 55 years of age and over 800 male subjects aged 10 to 18 years.

In clinical trials, more than 99% of initially seronegative subjects had seroconverted to both HPV types 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.

In a study which included women from 15 to 25 years of age at the time of vaccination, the persistence of the immune response against HPV-16 and HPV-18 was demonstrated up to 113 months after administration of the first vaccine dose.

In a pooled analysis (HPV-029,-30 & -48), 99.7% and 100% of females aged 9 years seroconverted to HPV types 16 and 18, respectively after the third dose (at month 7) with GMTs at least 1.4-fold and 2.4-fold higher as compared to females aged 10-14 years and 15 to 25 years, respectively.

In two clinical trials (HPV-012 & -013) performed in girls aged 10 to 14 years, all subjects seroconverted to both HPV types 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.

In clinical trials (HPV-070 and HPV-048) performed in girls aged 9 to 14 years receiving a 2-dose schedule (0, 6 months or 0, 12 months) and young women aged 15-25 years receiving **Cervarix** according to the standard 0, 1,6 months schedule, all subjects seroconverted to both HPV types 16 and 18 one month after the second dose. The immune response after 2 doses in females aged 9 to 14 years was non-inferior to the response after 3 doses in women aged 15 to 25 years.

On the basis of these immunogenicity data, the efficacy of **Cervarix** is inferred from 9 to 14 years of age.

In another clinical trial 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.

The administration of a challenge dose of **Cervarix** after a mean of 6.8 years following the first vaccination elicited an anamnestic immune response to HPV-16 and HPV-18 at day 7. One month after the challenge dose, GMTs exceeded those observed one month after the primary vaccination course.

Immunogenicity in women aged 26 years and older

In the Phase III study (HPV-015) in women 26 years and older, at the 48-month time point, i.e. 42 months after completion of the full vaccination course, 100% and 99.4% of initially seronegative women remained seropositive for anti-HPV-16 and anti-HPV-18 antibodies, respectively. All initially seropositive women remained seropositive for both anti-HPV-16 and anti-HPV-18 antibodies. Antibody titers peaked at month 7 then gradually declined up to month 18 and stabilized to reach a plateau up to month 48.

Immunogenicity in males aged 10 to 18 years

Immunogenicity in males was assessed in 2 clinical trials HPV-011 (N=173) and HPV-040 (N=556). The data showed comparable immunogenicity in males and females. In study HPV-011, all subjects seroconverted to both HPV-16 and 18 and GMT levels were non inferior to those observed in females aged 15 to 25 years in study HPV-012.

Bridging of clinical efficacy against anal lesions and cancers

No efficacy study against anal premalignant lesions has been conducted with **Cervarix**. However, studies conducted in girls aged 9 to 14 years (study HPV-071) and in women aged 18 to 45 years (study HPV-010) have consistently shown a higher immune response with **Cervarix** than with the comparator for which efficacy data against anal premalignant lesions are conclusive and have shown protection.

Immunogenicity in HIV infected women

In study HPV-020, conducted in South Africa, 22 HIV uninfected and 42 HIV infected subjects (WHO clinical stage 1; ATP cohort for immunogenicity) received **Cervarix**. All subjects were seropositive in the ELISA assay to both HPV 16 and 18 one month after the third dose (at Month 7) and the seropositivity for HPV 16 and 18 was maintained up to Month 12. The GMTs appeared to be lower in the HIV infected group (non overlapping 95% confidence interval). The clinical relevance of this observation is unknown. Functional antibodies were not determined. No information exists about protection against persistent infection or precancerous lesions among HIV infected women.

### 5.2 Pharmacokinetic properties

Not applicable.

### 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).

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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride
Sodium dihydrogen phosphate dihydrate
Water for injections

For adjuvants, see section 2.

### 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 – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

**Cervarix** should be administered as soon as possible after being removed from the refrigerator.

However, for the monodose and multidose containers, the stability has been demonstrated when stored outside the refrigerator for up to 3 days at temperatures between 8°C and 25°C or for up to 1 day at temperatures between 25°C and 37°C. If not used at the end of this period the vaccine should be discarded.

*Multidose vial*

For storage condition after first opening see section Special precautions for disposal and other handling.

### 6.5 Nature and contents of container

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

Multidose presentation: 2 doses
1 ml of suspension in a vial (type I glass) for 2 doses with a stopper (rubber butyl) - pack sizes of 1, 10 and 100.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

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

The content of the 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.

Multidose vial

After first opening of the multidose vial, immediate use is recommended.
If not used immediately, the multidose vial must be discarded at the end of each immunization session or after 6 hours from first opening, whichever comes first. The remaining vaccine should be maintained between +2°C to +8°C and protected from the sunlight.

When using a multidose vial, each dose should be drawn with a sterile needle and syringe. As with other vaccines, a dose of vaccine should be withdrawn under aseptic conditions and precautions taken to avoid contamination of the contents.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### 6.7 Vaccine Vial Monitor (see VVM pictogram at the end of the leaflet)

The Vaccine Vial Monitor (VVM) is either part of the label or the vial cap used for all **Cervarix** batches supplied by GlaxoSmithKline Biologicals. The colour dot that appears on the label of the vial for 1 dose (0.5 ml) or on the vial cap for 2 doses (1 ml) of vaccine is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the glass container should be discarded.

It is absolutely critical to ensure that the storage conditions specified above (in particular the cold chain) are complied with. GlaxoSmithKline Biologicals will assume no liability in the event **Cervarix** has not been stored in compliance with the storage instructions.

Inner square lighter than outer circle. **If the expiry date has not been passed, USE the vaccine.**

At a later time, inner square still lighter than outer circle. **If the expiry date has not been passed, USE the vaccine.**

**Discard point:** Inner square matches colour of outer circle. **DO NOT use the vaccine**.

**Beyond the discard point**: Inner square darker than outer ring. **DO NOT use the vaccine**.

For further information, please contact the manufacturer.



| |
|---|
| **WHO Product Information**<br>Version number: [GDS24/WHO Product Information 08] / Date of issue:<br>©[2017] GSK group of companies or its licensor |
| **Manufacturer:**<br>*GlaxoSmithKline Biologicals s.a.*<br>Rue de l'Institut 89, B-1330 Rixensart, Belgium.<br>Tel : (32) 2 656 81 11  Fax : (32) 2 656 80 00 |

# WHO LEAFLET

## DESCRIPTION

**Cervarix**, suspension for injection
Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

1 dose (0.5 ml) contains:

| | |
|---|---|
| Human Papillomavirus[1] type 16 L1 protein[2,3,4] | 20 micrograms |
| Human Papillomavirus[1] type 18 L1 protein[2,3,4] | 20 micrograms |

[1]Human Papillomavirus = HPV

[2]adjuvanted by AS04 containing:

| | |
|---|---|
| 3-*O*-desacyl-4'- monophosphoryl lipid A (MPL)[3] | 50 micrograms |
| [3]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$) | 0.5 milligrams $Al^{3+}$ in total |

[4]L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system which uses Hi-5 Rix4446 cells derived from *Trichoplusia ni*.

Excipients: Sodium chloride, sodium dihydrogen phosphate dihydrate, water for injections

## ADMINISTRATION

**Cervarix** is for intramuscular injection in the deltoid region (see also sections IMMUNIZATION SCHEDULE and PRECAUTIONS).

**Cervarix** should under no circumstances be administered intravascularly or intradermally. No data are available on subcutaneous administration of **Cervarix** (see section PRECAUTIONS).

If **Cervarix** is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites (see section IMMUNIZATION SCHEDULE).

**Cervarix** is a turbid white suspension. A fine white deposit with a clear colourless supernatant may be observed upon storage of the vial. This does not constitute a sign of deterioration.

The content of the 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.

<u>Multidose vial</u>

After first opening of the **multidose** vial, immediate use is recommended.
If not used immediately, the multidose vial must be discarded at the end of each immunization session or after 6 hours from first opening, whichever comes first. The remaining vaccine should be maintained between +2°C to +8°C and protected from the sunlight.

When using a multidose vial, each dose should be drawn with a sterile needle and syringe. As with other vaccines, a dose of vaccine should be withdrawn under aseptic conditions and precautions taken to avoid contamination of the contents.

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

**IMMUNIZATION SCHEDULE**

**Cervarix** is a vaccine for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic Human Papillomavirus (HPV) types. See sections PRECAUTIONS and PHARMACOLOGICAL PROPERTIES for important information on the data that support this indication.

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

The vaccination schedule depends on the age of the subject.

| **Age at the time of the first injection** | **Immunization and schedule** |
|---|---|
| 9 to and including 14 years* | Two doses each of 0.5 ml.<br>The second dose given between 5 and 13 months after the first dose |
| From 15 years and above | Three doses each of 0.5 ml at 0, 1, 6 months** |

*If the second vaccine dose is administered before the 5$^{th}$ month after the first dose, a third dose should always be administered.
**If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose.

The need for a booster dose has not been established (see section PHARMACOLOGICAL PROPERTIES).

It is recommended that subjects who receive a first dose of **Cervarix** complete the vaccination course with **Cervarix** (see section PRECAUTIONS).

*Paediatric population (children < 9 years of age)*
**Cervarix** is not recommended for use in children below 9 years of age due to lack of data on safety and immunogenicity in this age-group.

In all clinical trials individuals who had received immunoglobulin or blood-derived products within 3 months prior to the first vaccine dose were excluded.

*Use with other vaccines*

**Cervarix** may be administered concomitantly with:
- a combined booster vaccine containing diphtheria (d), tetanus (T) and pertussis [acellular] (pa) with or without inactivated poliomyelitis (IPV), (dTpa, dTpa-IPV vaccines),

- a combined hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (HAB vaccine).

If **Cervarix** is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

*Use with hormonal contraceptive*

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

*Use with systemic immunosuppressive medicinal products*

See section PRECAUTIONS.

**SIDE EFFECTS**

**Summary of safety profile**
In clinical studies that enrolled girls and women aged from 10 up to 72 years (of which 79.2% were aged 10-25 years at the time of enrolment), **Cervarix** was administered to 16,142 females whilst 13,811 females received control. These subjects were followed for serious adverse events over the entire study period. In a pre-defined subset of subjects (**Cervarix** = 8,130 versus control = 5,786), adverse events were followed for 30 days after each injection. In two clinical studies that enrolled males aged 10 to 18 years, 2,617 males received **Cervarix** and were followed-up with active safety surveillance.

The most common adverse 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.

**Tabulated list of adverse reactions**
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)

| System Organ Class | Frequency | Adverse reactions |
|---|---|---|
| **Clinical trials** | | |
| Infections and infestations | Uncommon | Upper respiratory tract infection |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness |
| Gastrointestinal disorders | Common | Gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain |
| Skin and subcutaneous tissue disorders | Common | Itching/pruritus, rash, urticaria |
| Musculoskeletal and connective tissue 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 |
| **Post-marketing experience** | | |
| Blood and lymphatic system disorders | Not known* | Lymphadenopathy |
| Immune system disorders | Not known* | Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema |
| Nervous system disorders | Not known* | Syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements (see section PRECAUTIONS) |

*Because these events were reported spontaneously, it is not possible to reliably estimate their frequency

In clinical trials a similar safety profile has been observed in subjects with prior or current HPV infection as compared to subjects negative for oncogenic HPV DNA or seronegative for HPV-16 and HPV-18 antibodies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

**CONTRAINDICATIONS**

Hypersensitivity to the active substances or to any of the excipients listed in section DESCRIPTION.

**PRECAUTIONS**

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

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

Administration of **Cervarix** should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a cold, is not a contraindication for immunization.

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

As with 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** will only protect against diseases that are caused by HPV types 16 and 18 and to some extent against diseases caused by certain other oncogenic related HPV types (see section PHARMACOLOGICAL PROPERTIES). Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.

The vaccine is for prophylactic use only and has no effect on active HPV infections or established clinical disease. The vaccine has not been shown to have a therapeutic effect. The vaccine is therefore not indicated for treatment of cervical cancer or cervical intraepithelial neoplasia (CIN). It is also not intended to prevent progression of other established HPV-related lesions or existing HPV infections with vaccine or non-vaccine types (see section PHARMACOLOGICAL PROPERTIES "Efficacy in women with evidence of HPV-16 or HPV-18 infection at study entry.").

Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100% effective and **Cervarix** will not provide protection against every HPV type, or against existing HPV infections, routine cervical screening remains critically important and should follow local recommendations.

Duration of protection has not fully been established. Timing and need of booster dose(s) has not been established.

Except for asymptomatic human immunodeficiency virus (HIV) infected subjects for whom limited immunogenicity data are available (see section PHARMACOLOGICAL PROPERTIES), there are no data on the use of **Cervarix** in subjects with impaired immune responsiveness such as patients receiving immunosuppressive treatment. As with other vaccines, an adequate immune response may not be elicited in these individuals.

There are no safety, immunogenicity or efficacy data to support interchangeability of **Cervarix** with other HPV vaccines.

***Pregnancy and lactation***

Pregnancy

Specific studies of the vaccine in pregnant women were not conducted. Data in pregnant women collected as part of pregnancy registries, epidemiological studies and inadvertent exposure during clinical trials are insufficient to conclude whether or not vaccination with **Cervarix** affects the risk of adverse pregnancy outcomes including spontaneous abortion.
However, during the clinical development program, a total of 10,476 pregnancies were reported including 5,387 in women who had received **Cervarix**. Overall, the proportions of pregnant subjects who experienced specific outcomes (e.g., normal infant, abnormal infants including congenital anomalies, premature birth, and spontaneous abortion) were similar between treatment groups.

Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development (see subsection PRECLINICAL SAFETY DATA).

As a precautionary measure, it is preferable to avoid the use of **Cervarix** during pregnancy. Women who are pregnant or trying to become pregnant, are advised to postpone or interrupt vaccination until completion of pregnancy.

Breast-feeding

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.

Fertility

No fertility data are available.

***Effects on ability to drive and use machines***

No studies on the effects on the ability to drive or use machines have been performed. However, some of the effects mentioned under section SIDE EFFECTS may temporarily affect the ability to drive or use machines.

***Overdose***

No case of overdose has been reported.

***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).

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.

***Incompatibilities***

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

**PHARMACOLOGICAL PROPERTIES**

For this section see WHO Product Information on the WHO website

**STORAGE**

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

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

**Cervarix** should be administered as soon as possible after being removed from the refrigerator.

However, for the monodose and multidose containers, the stability has been demonstrated when stored outside the refrigerator for up to 3 days at temperatures between 8°C and 25°C or for up to 1 day at temperatures between 25°C and 37°C. If not used at the end of this period the vaccine should be discarded.

*Multidose vial*

For storage condition after first opening see section ADMINISTRATION.

**PRESENTATION**

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

Multidose presentation: 2 doses
1 ml of suspension in a vial (type I glass) for 2 doses with a stopper (rubber butyl) - pack sizes of 1, 10 and 100.

Not all pack sizes may be marketed.

**Vaccine Vial Monitor (see VVM pictogram at the end of the leaflet)**

The Vaccine Vial Monitor (VVM) is either part of the label or the vial cap used for all **Cervarix** batches supplied by GlaxoSmithKline Biologicals. The colour dot that appears on the label of the vial for 1 dose (0.5 ml) or on the vial cap for 2 doses (1 ml) of vaccine is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the glass container should be discarded.

It is absolutely critical to ensure that the storage conditions specified above (in particular the cold chain) are complied with. GlaxoSmithKline Biologicals will assume no liability in the event **Cervarix** has not been stored in compliance with the storage instructions.

Inner square lighter than outer circle. **If the expiry date has not been passed, USE the vaccine.**

At a later time, inner square still lighter than outer circle. **If the expiry date has not been passed, USE the vaccine.**

**Discard point:** Inner square matches colour of outer circle. **DO NOT use the vaccine**.

**Beyond the discard point**: Inner square darker than outer ring. **DO NOT use the vaccine**.

For further information, please contact the manufacturer.



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