

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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

¹Human Papillomavirus = HPV

²adjuvanted by AS04 containing:

3-*O*-desacyl-4'-monophosphoryl lipid A (MPL)³ 50 micrograms

³adsorbed on aluminium hydroxide, hydrated (Al(OH)₃) 0.5 milligrams Al³⁺ in total

⁴L1 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 a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

Turbid white suspension. Upon storage, a fine white deposit with a clear colourless supernatant may be observed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cervarix is a vaccine for the prevention of premalignant cervical lesions and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18 (see section 5.1).

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

See section 5.1 for information on the evidence that supports the efficacy of Cervarix in prevention of premalignant cervical lesions associated with HPV-16 and/or HPV-18.

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

4.2 Posology and method of administration

The recommended vaccination schedule is 0, 1, 6 months.

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 3-dose vaccination course with Cervarix (see section 4.4).

Girls aged less than 10 years: Cervarix is not recommended for use in girls below 10 years of age due to lack of data on safety and immunogenicity in this age-group.

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

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

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 immunisation.

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 event following the administration of the vaccine.

Cervarix 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.

Vaccination is not a substitute for regular cervical screening or for precautions against exposure to HPV and sexually transmitted diseases.

As with any vaccine, a protective immune response may not be elicited in all vaccinees. Cervarix protects against disease caused by HPV types 16 and 18. Other oncogenic HPV types can also cause cervical cancer and therefore routine cervical screening remains critically important and should follow local recommendations.

Cervarix has not been shown to have a therapeutic effect. The vaccine is therefore not indicated for treatment of cervical cancer, cervical intraepithelial neoplasia (CIN) or any other established HPV-related lesions.

Cervarix does not prevent HPV-related lesions in women who are infected with HPV-16 or HPV-18 at the time of vaccination.

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

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. 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 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), with no clinically relevant interference with antibody response to any of the components of either vaccine. The sequential administration of combined dTpa-IPV followed by Cervarix one month later tended to elicit lower anti-HPV-16 and anti-HPV-18 GMTs as compared to Cervarix alone. The clinical significance of this observation is 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.

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 medicinal products

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

4.6 Pregnancy and lactation

Specific studies of the vaccine in pregnant women were not conducted. During the pre-licensure clinical development program, a total of 1,737 pregnancies were reported including 870 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).

These data are insufficient to recommend use of Cervarix during pregnancy. Vaccination should, therefore, be postponed until after completion of pregnancy.

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.

4.7 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.

4.8 Undesirable effects

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 subjects whilst 13,811 subjects 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.

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.

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

Frequencies are reported as:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

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

Infections and infestations:

Uncommon: upper respiratory tract infection

General disorders and administration site conditions:

Very common: injection site reactions including pain, redness, swelling; fatigue

Common: fever ($\geq 38^{\circ}\text{C}$)

Uncommon: other injection site reactions such as induration, local paraesthesia

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.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Papillomavirus vaccines, ATC code: J07BM02

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. Animal studies have shown that the efficacy of L1 VLP vaccines is largely mediated by the development of a humoral immune response.

HPV-16 and HPV-18 are responsible for approximately 70% of cervical cancers across all regions worldwide.

Clinical studies

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.

The phase II trial (study 001/007) enrolled only women who:

- Were tested negative for oncogenic HPV DNA of types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
- Were seronegative for HPV-16 and HPV-18 and
- Had normal cytology

The primary efficacy endpoint was incident infection with HPV-16 and/or HPV-18. Twelve-month persistent infection was evaluated as additional efficacy endpoint.

The phase III trial (study 008) enrolled women without pre-screening for the presence of HPV infection, i.e. regardless of baseline cytology and HPV serological and DNA status.

The primary efficacy endpoint was CIN2+ associated with HPV-16 and/or HPV-18. The secondary endpoints included 12-month persistent infection.

Cervical Intraepithelial Neoplasia (CIN) grade 2 and 3 was used in the clinical trials as a surrogate marker for cervical cancer.

The term “pre-malignant cervical lesions” in section 4.1 corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN 2/3).

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). There were five cases of 12-month persistent HPV-16/18 infection (4 HPV-16; 1 HPV-18) in the control group and one HPV-16 case in the vaccine group in study 001. In study 007 the efficacy of Cervarix against 12-month persistent HPV-16/18 infection was 100% (95% CI: 80.5; 100). There were sixteen cases of persistent HPV-16 infection, and five cases of persistent HPV-18 infection, all in the control group.

Prophylactic efficacy in women naïve to HPV-16 and/or HPV-18

In study 008 the primary analyses of efficacy were conducted in the total vaccinated cohort (TVC-1). This cohort included only women who were HPV DNA negative and seronegative to the relevant HPV type (HPV-16 or HPV-18) at study entry and had received at least one dose of Cervarix or the control. Women with high-grade or missing cytology (0.5%) were excluded from the efficacy analysis.

Overall, 74.0% of women enrolled were naïve to both HPV-16 and HPV-18 at study entry.

The efficacy of Cervarix in the prevention of CIN2+ associated with HPV-16 and/or HPV-18 as assessed up to 15 months after the last dose of vaccine or control and the rates of 12-month persistent infection in the TVC-1 cohort are presented in the table below:

Study 008	Cervarix		Control		Efficacy (97.9% CI)
	N	n	N	n	
CIN2+ (primary endpoint)					
HPV-16 and/or 18*	7788	2	7838	21	90.4 (53.4; 99.3)
HPV-16	6701	1	6717	15	93.3 (47.0; 99.9)
HPV-18	7221	1	7258	6	83.3 (<0.0; 99.9)
12-month persistent infection (secondary endpoint)					
HPV-16 and/or 18*	3386	11	3437	46	75.9 (47.7; 90.2)

HPV-16	2945	7	2972	35	79.9 (48.3; 93.8)
HPV-18	3143	4	3190	12	66.2 (<0.0; 94.0)
N = number of subjects included in each group of TVC-1 cohort					
n = number of cases					
*protocol-specified endpoints					

All endpoints reached statistical significance for HPV-16. For HPV-18, the difference between the vaccine and control groups was not statistically significant for CIN2+ and 12 month persistent infection (TVC-1 cohort). However, in a pre-specified analysis (TVC-2) that was identical to the TVC-1 analysis except that it excluded women with abnormal cytology at study entry, the 12 month persistent infection endpoint for HPV-18 reached statistical significance with vaccine efficacy of 89.9% (97.9% CI: 11.3; 99.9). One case was observed in the vaccine group versus 10 cases in the control group.

Several of the CIN2+ lesions contained multiple oncogenic types (including non-vaccine HPV types). An additional analysis was conducted to determine vaccine efficacy against lesions likely to be causally associated with HPV-16 and/or HPV-18. This post-hoc analysis (clinical case assignment) assigned causal association of an HPV type with the lesion based on the presence of the HPV type in cytology samples prior to detection of the lesion. Based on this case assignment, the analysis excluded 3 CIN2+ cases (2 in the vaccine group and 1 in the control group) which were not considered to be causally associated with HPV-16 or HPV-18 infections acquired during the trial. Based on this analysis there were no cases in the vaccine group and 20 cases in the control group (Efficacy 100%; 97.9% CI: 74.2; 100).

Prophylactic efficacy in women with current or prior infection

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 with one of the vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining HPV type.

In study 008, approximately 26% of women had evidence of current and/or prior infection. Twenty percent of women had evidence of prior infection (i.e. HPV-16 and/or HPV-18 seropositive). Seven percent of women were infected at time of vaccination (i.e. HPV-16 and/or HPV-18 DNA positive) of which only 0.5% were DNA positive for both types.

Immunogenicity

No minimal antibody level associated with protection against CIN of grade 2 or 3 or against persistent infection associated with vaccine HPV types has been identified for HPV vaccines.

The antibody response to HPV-16 and HPV-18 was measured using a type-specific ELISA which was shown to correlate with the pseudovirion-based neutralisation assay.

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 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.

Study 001/007, which included women from 15 to 25 years of age at the time of vaccination, evaluated the immune response against HPV-16 and HPV-18 up to 76 months post dose 1. 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 76). 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 and >98% of the women were still seropositive for both antigens. In study 008, immunogenicity at month 7 was similar to the response observed in study 001.

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 from young adult women to adolescents

In two clinical trials performed in girls and adolescents 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. On the basis of these immunogenicity data, the efficacy of Cervarix is 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).

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 (NaCl)
Sodium dihydrogen phosphate dihydrate ($\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$)
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

4 years.

Cervarix should be administered as soon as possible after being removed from the refrigerator. However, stability data generated indicate that Cervarix presented in monodose containers remains stable and can be administered in case it has been stored outside the refrigerator up to three days at temperatures between 8°C and 25°C or up to one day at temperatures between 25°C and 37°C.

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.

6.5 Nature and contents of container

0.5 ml of suspension in a vial (type I glass) for 1 dose with a stopper (rubber butyl) in 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.

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/419/001
EU/1/07/419/002
EU/1/07/419/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2007.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.ema.europa.eu/>.

1. NAME OF THE MEDICINAL PRODUCT

Cervarix suspension for injection, multidose
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

¹Human Papillomavirus = HPV

²adjuvanted by AS04 containing:

3- <i>O</i> -desacyl-4'-monophosphoryl lipid A (MPL) ³	50 micrograms
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³ adsorbed on aluminium hydroxide, hydrated (Al(OH) ₃)	0.5 milligrams Al ³⁺ in total
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⁴L1 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*.

This is a multidose container. See section 6.5 for the number of doses per vial.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

Turbid white suspension. Upon storage, a fine white deposit with a clear colourless supernatant may be observed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cervarix is a vaccine for the prevention of premalignant cervical lesions and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18 (see section 5.1).

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

See section 5.1 for information on the evidence that supports the efficacy of Cervarix in prevention of premalignant cervical lesions associated with HPV-16 and/or HPV-18.

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

4.2 Posology and method of administration

The recommended vaccination schedule is 0, 1, 6 months.

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 3-dose vaccination course with Cervarix (see section 4.4).

Girls aged less than 10 years: Cervarix is not recommended for use in girls below 10 years of age due to lack of data on safety and immunogenicity in this age-group.

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

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

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 immunisation.

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 event following the administration of the vaccine.

Cervarix 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.

Vaccination is not a substitute for regular cervical screening or for precautions against exposure to HPV and sexually transmitted diseases.

As with any vaccine, a protective immune response may not be elicited in all vaccinees. Cervarix protects against disease caused by HPV types 16 and 18. Other oncogenic HPV types can also cause cervical cancer and therefore routine cervical screening remains critically important and should follow local recommendations.

Cervarix has not been shown to have a therapeutic effect. The vaccine is therefore not indicated for treatment of cervical cancer, cervical intraepithelial neoplasia (CIN) or any other established HPV-related lesions.

Cervarix does not prevent HPV-related lesions in women who are infected with HPV-16 or HPV-18 at the time of vaccination.

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

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. 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 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), with no clinically relevant interference with antibody response to any of the components of either vaccine. The sequential administration of combined dTpa-IPV followed by Cervarix one month later tended to elicit lower anti-HPV-16 and anti-HPV-18 GMTs as compared to Cervarix alone. The clinical significance of this observation is 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.

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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 medicinal products

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

4.6 Pregnancy and lactation

Specific studies of the vaccine in pregnant women were not conducted. During the pre-licensure clinical development program, a total of 1,737 pregnancies were reported including 870 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).

These data are insufficient to recommend use of Cervarix during pregnancy. Vaccination should, therefore, be postponed until after completion of pregnancy.

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.

4.7 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.

4.8 Undesirable effects

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Very common: myalgia

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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.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Papillomavirus vaccines, ATC code: J07BM02

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. Animal studies have shown that the efficacy of L1 VLP vaccines is largely mediated by the development of a humoral immune response.

HPV-16 and HPV-18 are responsible for approximately 70% of cervical cancers across all regions worldwide.

Clinical studies

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.

The phase II trial (study 001/007) enrolled only women who:

- Were tested negative for oncogenic HPV DNA of types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
- Were seronegative for HPV-16 and HPV-18 and
- Had normal cytology

The primary efficacy endpoint was incident infection with HPV-16 and/or HPV-18. Twelve-month persistent infection was evaluated as additional efficacy endpoint.

The phase III trial (study 008) enrolled women without pre-screening for the presence of HPV infection, i.e. regardless of baseline cytology and HPV serological and DNA status.

The primary efficacy endpoint was CIN2+ associated with HPV-16 and/or HPV-18. The secondary endpoints included 12-month persistent infection.

Cervical Intraepithelial Neoplasia (CIN) grade 2 and 3 was used in the clinical trials as a surrogate marker for cervical cancer.

The term “pre-malignant cervical lesions” in section 4.1 corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN 2/3).

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). There were five cases of 12-month persistent HPV-16/18 infection (4 HPV-16; 1 HPV-18) in the control group and one HPV-16 case in the vaccine group in study 001. In study 007 the efficacy of Cervarix against 12-month persistent HPV-16/18 infection was 100% (95% CI: 80.5; 100). There were sixteen cases of persistent HPV-16 infection, and five cases of persistent HPV-18 infection, all in the control group.

Prophylactic efficacy in women naïve to HPV-16 and/or HPV-18

In study 008 the primary analyses of efficacy were conducted in the total vaccinated cohort (TVC-1). This cohort included only women who were HPV DNA negative and seronegative to the relevant HPV type (HPV-16 or HPV-18) at study entry and had received at least one dose of Cervarix or the control. Women with high-grade or missing cytology (0.5%) were excluded from the efficacy analysis.

Overall, 74.0% of women enrolled were naïve to both HPV-16 and HPV-18 at study entry.

The efficacy of Cervarix in the prevention of CIN2+ associated with HPV-16 and/or HPV-18 as assessed up to 15 months after the last dose of vaccine or control and the rates of 12-month persistent infection in the TVC-1 cohort are presented in the table below:

Study 008	Cervarix		Control		Efficacy (97.9% CI)
	N	n	N	n	
CIN2+ (primary endpoint)					
HPV-16 and/or 18*	7788	2	7838	21	90.4 (53.4; 99.3)
HPV-16	6701	1	6717	15	93.3 (47.0; 99.9)
HPV-18	7221	1	7258	6	83.3 (<0.0; 99.9)

12-month persistent infection (secondary endpoint)					
HPV-16 and/or 18*	3386	11	3437	46	75.9 (47.7; 90.2)
HPV-16	2945	7	2972	35	79.9 (48.3; 93.8)
HPV-18	3143	4	3190	12	66.2 (<0.0; 94.0)
N = number of subjects included in each group of TVC-1 cohort					
n = number of cases					
*protocol-specified endpoints					

All endpoints reached statistical significance for HPV-16. For HPV-18, the difference between the vaccine and control groups was not statistically significant for CIN2+ and 12 month persistent infection (TVC-1 cohort). However, in a pre-specified analysis (TVC-2) that was identical to the TVC-1 analysis except that it excluded women with abnormal cytology at study entry, the 12 month persistent infection endpoint for HPV-18 reached statistical significance with vaccine efficacy of 89.9% (97.9% CI: 11.3; 99.9). One case was observed in the vaccine group versus 10 cases in the control group.

Several of the CIN2+ lesions contained multiple oncogenic types (including non-vaccine HPV types). An additional analysis was conducted to determine vaccine efficacy against lesions likely to be causally associated with HPV-16 and/or HPV-18. This post-hoc analysis (clinical case assignment) assigned causal association of an HPV type with the lesion based on the presence of the HPV type in cytology samples prior to detection of the lesion. Based on this case assignment, the analysis excluded 3 CIN2+ cases (2 in the vaccine group and 1 in the control group) which were not considered to be causally associated with HPV-16 or HPV-18 infections acquired during the trial. Based on this analysis there were no cases in the vaccine group and 20 cases in the control group (Efficacy 100%; 97.9% CI: 74.2; 100).

Prophylactic efficacy in women with current or prior infection

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 with one of the vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining HPV type.

In study 008, approximately 26% of women had evidence of current and/or prior infection. Twenty percent of women had evidence of prior infection (i.e. HPV-16 and/or HPV-18 seropositive). Seven percent of women were infected at time of vaccination (i.e. HPV-16 and/or HPV-18 DNA positive) of which only 0.5% were DNA positive for both types.

Immunogenicity

No minimal antibody level associated with protection against CIN of grade 2 or 3 or against persistent infection associated with vaccine HPV types has been identified for HPV vaccines.

The antibody response to HPV-16 and HPV-18 was measured using a type-specific ELISA which was shown to correlate with the pseudovirion-based neutralisation assay.

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 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.

Study 001/007, which included women from 15 to 25 years of age at the time of vaccination, evaluated the immune response against HPV-16 and HPV-18 up to 76 months post dose 1.

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 76). 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 and >98% of the women were still seropositive for both antigens. In study 008, immunogenicity at month 7 was similar to the response observed in study 001.

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 from young adult women to adolescents

In two clinical trials performed in girls and adolescents 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. On the basis of these immunogenicity data, the efficacy of Cervarix is 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).

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 (NaCl)
Sodium dihydrogen phosphate dihydrate ($\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$)
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

3 years.

After first opening, immediate use is recommended. If not used immediately, the vaccine should be stored in a refrigerator (2°C – 8°C). If not used within 6 hours it should be discarded.

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.

For storage after first opening, see section 6.3.

6.5 Nature and contents of container

1 ml of suspension in a vial (type I glass) for 2 doses with a stopper (rubber butyl) in 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.

When using a multidose vial, each 0.5 ml dose should be withdrawn using a sterile needle and syringe; precautions should be taken to avoid contamination of the contents.

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.

Rue de l'Institut 89

B-1330 Rixensart, Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/419/010

EU/1/07/419/011

EU/1/07/419/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2007.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu/>.

1. NAME OF THE MEDICINAL PRODUCT

Cervarix suspension for injection in pre-filled syringe
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

¹Human Papillomavirus = HPV

²adjuvanted by AS04 containing:

3-*O*-desacyl-4'-monophosphoryl lipid A (MPL)³ 50 micrograms

³adsorbed on aluminium hydroxide, hydrated (Al(OH)₃) 0.5 milligrams Al³⁺ in total

⁴L1 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 a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.

Turbid white suspension. Upon storage, a fine white deposit with a clear colourless supernatant may be observed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cervarix is a vaccine for the prevention of premalignant cervical lesions and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18 (see section 5.1).

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

See section 5.1 for information on the evidence that supports the efficacy of Cervarix in prevention of premalignant cervical lesions associated with HPV-16 and/or HPV-18.

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

4.2 Posology and method of administration

The recommended vaccination schedule is 0, 1, 6 months.

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 3-dose vaccination course with Cervarix (see section 4.4).

Girls aged less than 10 years: Cervarix is not recommended for use in girls below 10 years of age due to lack of data on safety and immunogenicity in this age-group.

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

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

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 immunisation.

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 event following the administration of the vaccine.

Cervarix 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.

Vaccination is not a substitute for regular cervical screening or for precautions against exposure to HPV and sexually transmitted diseases.

As with any vaccine, a protective immune response may not be elicited in all vaccinees. Cervarix protects against disease caused by HPV types 16 and 18. Other oncogenic HPV types can also cause cervical cancer and therefore routine cervical screening remains critically important and should follow local recommendations.

Cervarix has not been shown to have a therapeutic effect. The vaccine is therefore not indicated for treatment of cervical cancer, cervical intraepithelial neoplasia (CIN) or any other established HPV-related lesions.

Cervarix does not prevent HPV-related lesions in women who are infected with HPV-16 or HPV-18 at the time of vaccination.

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

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. 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 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), with no clinically relevant interference with antibody response to any of the components of either vaccine. The sequential administration of combined dTpa-IPV followed by Cervarix one month later tended to elicit lower anti-HPV-16 and anti-HPV-18 GMTs as compared to Cervarix alone. The clinical significance of this observation is 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.

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 medicinal products

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

4.6 Pregnancy and lactation

Specific studies of the vaccine in pregnant women were not conducted. During the pre-licensure clinical development program, a total of 1,737 pregnancies were reported including 870 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).

These data are insufficient to recommend use of Cervarix during pregnancy. Vaccination should, therefore, be postponed until after completion of pregnancy.

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.

4.7 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.

4.8 Undesirable effects

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 subjects whilst 13,811 subjects 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.

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.

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

Frequencies are reported as:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

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

Infections and infestations:

Uncommon: upper respiratory tract infection

General disorders and administration site conditions:

Very common: injection site reactions including pain, redness, swelling; fatigue

Common: fever ($\geq 38^\circ\text{C}$)

Uncommon: other injection site reactions such as induration, local paraesthesia

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.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Papillomavirus vaccines, ATC code: J07BM02

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. Animal studies have shown that the efficacy of L1 VLP vaccines is largely mediated by the development of a humoral immune response.

HPV-16 and HPV-18 are responsible for approximately 70% of cervical cancers across all regions worldwide.

Clinical studies

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.

The phase II trial (study 001/007) enrolled only women who:

- Were tested negative for oncogenic HPV DNA of types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
- Were seronegative for HPV-16 and HPV-18 and
- Had normal cytology

The primary efficacy endpoint was incident infection with HPV-16 and/or HPV-18. Twelve-month persistent infection was evaluated as additional efficacy endpoint.

The phase III trial (study 008) enrolled women without pre-screening for the presence of HPV infection, i.e. regardless of baseline cytology and HPV serological and DNA status.

The primary efficacy endpoint was CIN2+ associated with HPV-16 and/or HPV-18. The secondary endpoints included 12-month persistent infection.

Cervical Intraepithelial Neoplasia (CIN) grade 2 and 3 was used in the clinical trials as a surrogate marker for cervical cancer.

The term “pre-malignant cervical lesions” in section 4.1 corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN 2/3).

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). There were five cases of 12-month persistent HPV-16/18 infection (4 HPV-16; 1 HPV-18) in the control group and one HPV-16 case in the vaccine group in study 001. In study 007 the efficacy of Cervarix against 12-month persistent HPV-16/18 infection was 100% (95% CI: 80.5; 100). There were sixteen cases of persistent HPV-16 infection, and five cases of persistent HPV-18 infection, all in the control group.

Prophylactic efficacy in women naïve to HPV-16 and/or HPV-18

In study 008 the primary analyses of efficacy were conducted in the total vaccinated cohort (TVC-1). This cohort included only women who were HPV DNA negative and seronegative to the relevant HPV type (HPV-16 or HPV-18) at study entry and had received at least one dose of Cervarix or the control. Women with high-grade or missing cytology (0.5%) were excluded from the efficacy analysis.

Overall, 74.0% of women enrolled were naïve to both HPV-16 and HPV-18 at study entry.

The efficacy of Cervarix in the prevention of CIN2+ associated with HPV-16 and/or HPV-18 as assessed up to 15 months after the last dose of vaccine or control and the rates of 12-month persistent infection in the TVC-1 cohort are presented in the table below:

Study 008	Cervarix		Control		Efficacy (97.9% CI)
	N	n	N	n	
CIN2+ (primary endpoint)					
HPV-16 and/or 18*	7788	2	7838	21	90.4 (53.4; 99.3)
HPV-16	6701	1	6717	15	93.3 (47.0; 99.9)
HPV-18	7221	1	7258	6	83.3 (<0.0; 99.9)
12-month persistent infection (secondary endpoint)					
HPV-16 and/or 18*	3386	11	3437	46	75.9 (47.7; 90.2)

HPV-16	2945	7	2972	35	79.9 (48.3; 93.8)
HPV-18	3143	4	3190	12	66.2 (<0.0; 94.0)
N = number of subjects included in each group of TVC-1 cohort					
n = number of cases					
*protocol-specified endpoints					

All endpoints reached statistical significance for HPV-16. For HPV-18, the difference between the vaccine and control groups was not statistically significant for CIN2+ and 12 month persistent infection (TVC-1 cohort). However, in a pre-specified analysis (TVC-2) that was identical to the TVC-1 analysis except that it excluded women with abnormal cytology at study entry, the 12 month persistent infection endpoint for HPV-18 reached statistical significance with vaccine efficacy of 89.9% (97.9% CI: 11.3; 99.9). One case was observed in the vaccine group versus 10 cases in the control group.

Several of the CIN2+ lesions contained multiple oncogenic types (including non-vaccine HPV types). An additional analysis was conducted to determine vaccine efficacy against lesions likely to be causally associated with HPV-16 and/or HPV-18. This post-hoc analysis (clinical case assignment) assigned causal association of an HPV type with the lesion based on the presence of the HPV type in cytology samples prior to detection of the lesion. Based on this case assignment, the analysis excluded 3 CIN2+ cases (2 in the vaccine group and 1 in the control group) which were not considered to be causally associated with HPV-16 or HPV-18 infections acquired during the trial. Based on this analysis there were no cases in the vaccine group and 20 cases in the control group (Efficacy 100%; 97.9% CI: 74.2; 100).

Prophylactic efficacy in women with current or prior infection

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 with one of the vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining HPV type.

In study 008, approximately 26% of women had evidence of current and/or prior infection. Twenty percent of women had evidence of prior infection (i.e. HPV-16 and/or HPV-18 seropositive). Seven percent of women were infected at time of vaccination (i.e. HPV-16 and/or HPV-18 DNA positive) of which only 0.5% were DNA positive for both types.

Immunogenicity

No minimal antibody level associated with protection against CIN of grade 2 or 3 or against persistent infection associated with vaccine HPV types has been identified for HPV vaccines.

The antibody response to HPV-16 and HPV-18 was measured using a type-specific ELISA which was shown to correlate with the pseudovirion-based neutralisation assay.

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 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.

Study 001/007, which included women from 15 to 25 years of age at the time of vaccination, evaluated the immune response against HPV-16 and HPV-18 up to 76 months post dose 1. 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 76). 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 and >98% of the women were still seropositive for both antigens. In study 008, immunogenicity at month 7 was similar to the response observed in study 001.

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 from young adult women to adolescents

In two clinical trials performed in girls and adolescents 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. On the basis of these immunogenicity data, the efficacy of Cervarix is 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).

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 (NaCl)
Sodium dihydrogen phosphate dihydrate ($\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$)
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

4 years.

Cervarix should be administered as soon as possible after being removed from the refrigerator. However, stability data generated indicate that Cervarix presented in monodose containers remains stable and can be administered in case it has been stored outside the refrigerator up to three days at temperatures between 8°C and 25°C or up to one day at temperatures between 25°C and 37°C.

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.

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 in pack sizes of 1 and 10.

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 syringe. This does not constitute a sign of deterioration.

The content of the syringe 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.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/419/004
EU/1/07/419/005
EU/1/07/419/006
EU/1/07/419/007
EU/1/07/419/008
EU/1/07/419/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2007.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu/>.

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURING AUTHORISATION
HOLDER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

GlaxoSmithKline Biologicals S.A.
89, rue de l'Institut
BE-1330 Rixensart
Belgium

GlaxoSmithKline Biologicals SA
Parc de la Noire Epine
rue Flemming
20-1300 Wavre
Belgium

GlaxoSmithKline Biologicals S.A.
Les Isnes
Rue Louis Genonceau, 13
BE-5023 Gembloux
Belgium

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Biologicals S.A.
89, rue de l'Institut
BE-1330 Rixensart
Belgium

B. CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

• **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 2 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 2 of the Risk Management Plan (RMP) presented in

Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

Official batch release: in accordance with Article 114 Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MONODOSE VIAL, PACK OF 1, 10, 100**

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) contains:

HPV type 16 L1 protein ^{1,2}	20 micrograms
HPV type 18 L1 protein ^{1,2}	20 micrograms

¹ adjuvanted by AS04 containing:
3-*O*-desacyl-4'-monophosphoryl lipid A (MPL)² 50 micrograms

²adsorbed on aluminium hydroxide, hydrated (Al(OH)₃) 0.5 milligrams Al³⁺ in total

3. LIST OF EXCIPIENTS

Sodium chloride
Sodium dihydrogen phosphate dihydrate
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
1 vial
1 dose (0.5 ml)

10 vials
10 x 1 dose (0.5 ml)

100 vials
100 x 1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Intramuscular use
Shake before use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/419/001 – pack of 1
EU/1/07/419/002 – pack of 10
EU/1/07/419/003 – pack of 100

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIDOSE VIAL, PACK OF 1, 10, 100**

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) contains:

HPV type 16 L1 protein ^{1,2}	20 micrograms
HPV type 18 L1 protein ^{1,2}	20 micrograms

¹ adjuvanted by AS04 containing: 3- <i>O</i> -desacyl-4'-monophosphoryl lipid A (MPL) ²	50 micrograms
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² adsorbed on aluminium hydroxide, hydrated (Al(OH) ₃)	0.5 milligrams Al ³⁺ in total
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3. LIST OF EXCIPIENTS

Sodium chloride
Sodium dihydrogen phosphate dihydrate
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
1 vial
2 doses (1 ml)

10 vials
10 x 2 doses (1 ml)

100 vials
100 x 2 doses (1 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Intramuscular use
Shake before use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening, use immediately or within 6 hours if stored in a refrigerator

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

Do not freeze

Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.

Rue de l'Institut 89

B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/419/010 – pack of 1

EU/1/07/419/011 – pack of 10

EU/1/07/419/012 – pack of 100

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED SYRINGE WITH OR WITHOUT NEEDLE, PACK OF 1, 10**

1. NAME OF THE MEDICINAL PRODUCT

Cervarix suspension for injection in pre-filled syringe
Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) contains:

HPV type 16 L1 protein ^{1,2}	20 micrograms
HPV type 18 L1 protein ^{1,2}	20 micrograms

¹ adjuvanted by AS04 containing:
3-*O*-desacyl-4'-monophosphoryl lipid A (MPL)² 50 micrograms

²adsorbed on aluminium hydroxide, hydrated (Al(OH)₃) 0.5 milligrams Al³⁺ in total

3. LIST OF EXCIPIENTS

Sodium chloride
Sodium dihydrogen phosphate dihydrate
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in pre-filled syringe
1 pre-filled syringe
1 dose (0.5 ml)

10 pre-filled syringes
10 x 1 dose (0.5 ml)

1 pre-filled syringe + 1 needle
1 dose (0.5 ml)

10 pre-filled syringes + 10 needles
10 x 1 dose (0.5 ml)

1 pre-filled syringe + 2 needles
1 dose (0.5 ml)

10 pre-filled syringes + 20 needles
10 x 1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Intramuscular use
Shake before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/419/008 – pack of 1 without needle
EU/1/07/419/009 – pack of 10 without needle
EU/1/07/419/004 – pack of 1 with 1 needle
EU/1/07/419/006 – pack of 10 with 10 needles
EU/1/07/419/005 – pack of 1 with 2 needles
EU/1/07/419/007 – pack of 10 with 20 needles

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
MONODOSE VIAL LABEL**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cervarix
Suspension for injection

I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
MULTIDOSE VIAL LABEL**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cervarix
Suspension for injection

I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 doses (1 ml)

6. OTHER

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE LABEL**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cervarix
Suspension for injection in pre-filled syringe

I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Cervarix suspension for injection

Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

Read all of this leaflet carefully before you start receiving this vaccine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Cervarix is and what it is used for
2. Before you receive Cervarix
3. How Cervarix is given
4. Possible side effects
5. How to store Cervarix
6. Further information

1. WHAT CERVARIX IS AND WHAT IT IS USED FOR

Cervarix is a vaccine intended to protect females against the diseases caused by infection with Human Papillomavirus (HPV) types 16 and 18.

These diseases include:

- cervical cancer (cancer of the cervix i.e. lower part of the uterus or womb),
- precancerous cervical lesions (changes in cells of the cervix that have a risk of turning into cancer).

Cervarix will not protect against all types of Human Papillomavirus. HPV types 16 and 18 are responsible for approximately 70% of cervical cancer cases.

When a female is vaccinated with Cervarix, the immune system (the body's natural defence system) will make antibodies against HPV types 16 and 18. In clinical trials Cervarix has been shown to prevent HPV types 16 and 18 related diseases in women 15-25 years of age. Cervarix also stimulates production of antibodies in females 10-14 years of age.

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

Cervarix is not used to treat HPV related diseases already present at the time of vaccination.

Cervarix should be used in accordance with official guidelines.

2. BEFORE YOU RECEIVE CERVARIX

Cervarix should not be given if
the person to be vaccinated:

- is allergic (hypersensitive) to any of the active substances or any of the other ingredients of Cervarix. The active substances and other ingredients of Cervarix are listed at the end of the leaflet (see section 6). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

- has a severe infection with a high temperature. It might be necessary to postpone the vaccination until recovery. A minor infection such as a cold should not be a problem, but talk to the doctor first.

Take special care with Cervarix

You should tell the doctor if the person to be vaccinated:

- has a bleeding problem or bruises easily.
- has any disease which reduces her resistance to infection such as HIV infection

As with all vaccines, Cervarix may not fully protect all people who are vaccinated.

Cervarix does not protect people from diseases caused by infection with HPV types 16 or 18 if they are already infected with Human Papillomavirus type 16 or 18 at the time of vaccination.

Although vaccination may protect you against cervical cancer, it is not a substitute for regular cervical screening. You should continue to follow your doctor's advice on cervical smear/Pap test (test to screen for changes in cells of the cervix caused by an HPV infection) and preventative and protective measures.

As Cervarix will not protect against all types of Human Papillomavirus, appropriate precautions against exposure to HPV and sexually transmitted diseases should continue to be used.

Cervarix will not protect against other diseases that are not caused by Human Papillomavirus.

The duration of protection after vaccination is currently unknown. In clinical trials, sustained protection has been observed in females aged 15 to 25 years for up to 6.4 years after the first dose. The need for booster dose(s) has not been investigated.

Using other medicines

Cervarix can be given with a combined booster vaccine containing diphtheria (d), tetanus (T) and pertussis [acellular] (pa) with or without inactivated poliomyelitis (IPV), (dTpa, dTpa -IPV vaccines), at a separate injection site (another part of your body, e.g. the other arm) during the same visit.

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

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

Please tell the doctor if the person to be vaccinated is taking or has recently taken any other medicines, including medicines obtained without a prescription or has recently received any other vaccine.

Pregnancy and breast-feeding

There are insufficient data concerning the use of Cervarix during pregnancy. If pregnancy occurs during the course of vaccination your doctor should be consulted. It is recommended to postpone vaccination until after completion of the pregnancy.

Ask your doctor for advice about breast-feeding before receiving Cervarix.

Driving and using machines

There is no information on the effect of Cervarix on your ability to drive or use machinery.

3. HOW CERVARIX IS GIVEN

The doctor or nurse will give Cervarix as an injection into the muscle of the upper arm.

Cervarix is intended for females from 10 years of age onwards. A total of three injections will be administered by your doctor or nurse according to the following schedule:

First injection: at chosen date
Second injection: 1 month after first injection
Third injection: 6 months after first injection

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

When Cervarix is given for the first dose, it is recommended that Cervarix (and not another vaccine against HPV) be given for the complete 3-dose vaccination course.

The vaccine should never be given into a vein.

If you forget a return visit for Cervarix:

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

If you do not finish the complete vaccination course of three injections, you may not get the best response and protection from the vaccination.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cervarix can cause side effects, although not everybody gets them.

Side effects that occurred during clinical trials with Cervarix were as follows:

- ◆ Very common (side effects which may occur in more than 1 per 10 doses of vaccine):
 - pain or discomfort at the injection site
 - redness or swelling at the injection site
 - headache
 - aching muscles, muscle tenderness or weakness (not caused by exercise)
 - tiredness

- ◆ Common (side effects which may occur in less than 1 per 10 but more than 1 per 100 doses of vaccine):
 - gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain
 - itching, red skin rash, hives (urticaria)
 - joint pain
 - fever ($\geq 38^{\circ}\text{C}$)

- ◆ Uncommon (side effects which may occur in less than 1 per 100 but more than 1 per 1,000 doses of vaccine):
 - upper respiratory tract infection (infection of the nose, throat or trachea)
 - dizziness
 - other injection site reactions such as hard lump, tingling or numbness.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CERVARIX

Keep out of the reach and sight of children.

Do not use Cervarix after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Store in the original package in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Cervarix contains

- The active substances are:

Human Papillomavirus ¹ type 16 L1 protein ^{2,3,4}	20 micrograms
Human Papillomavirus ¹ type 18 L1 protein ^{2,3,4}	20 micrograms

¹Human Papillomavirus = HPV

²adjuvanted by AS04 containing:

3- <i>O</i> -desacyl-4'- monophosphoryl lipid A (MPL) ³	50 micrograms
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³ adsorbed on aluminium hydroxide, hydrated (Al(OH) ₃)	0.5 milligrams Al ³⁺ in total
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⁴L1 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 the insect *Trichoplusia ni*.

- The other ingredients are sodium chloride (NaCl), sodium dihydrogen phosphate dihydrate (NaH₂PO₄·2 H₂O) and water for injections.

What Cervarix looks like and contents of the pack

Suspension for injection.

Cervarix is a turbid white suspension.

Cervarix is available in vials for 1 dose (0.5 ml) in packs of 1, 10 and 100.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

Luxembourg/Luxemburg
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

България

ГлаксоСмитКлайн ЕООД
ул. Димитър Манов бл.10
София 1408
Тел. + 359 2 953 10 34

Česká republika

GlaxoSmithKline s.r.o.
Tel: + 420 2 22 00 11 11
gsk.czmail@gsk.com

Danmark

GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
info@glaxosmithkline.dk

Deutschland

GlaxoSmithKline GmbH & Co. KG
Tel: + 49 (0)89 360448701
produkt.info@gsk.com

Eesti

GlaxoSmithKline Eesti OÜ
Tel: +372 667 6900
estonia@gsk.com

Ελλάδα

GlaxoSmithKline A.E.B.E
Τηλ: + 30 210 68 82 100

España

GlaxoSmithKline, S.A.
Tel: + 34 902 202 700
es-ci@gsk.com

France

Laboratoire GlaxoSmithKline
Tél: + 33 (0) 1 39 17 84 44
diam@gsk.com

Ireland

GlaxoSmithKline (Ireland) Ltd
Tel: + 353 (0)1 4955000

Ísland

GlaxoSmithKline ehf.
Sími: +354-530 3700

Italia

GlaxoSmithKline S.p.A.
Tel:+ 39 04 59 21 81 11

Κύπρος

GlaxoSmithKline (Cyprus) Ltd

Magyarország

GlaxoSmithKline Kft.
Tel.: + 36-1-2255300

Malta

GlaxoSmithKline Malta
Tel: + 356 21 238131

Nederland

GlaxoSmithKline BV
Tel: + 31 (0)30 69 38 100
nlinfo@gsk.com

Norge

GlaxoSmithKline AS
Tlf: + 47 22 70 20 00
firmapost@gsk.no

Österreich

GlaxoSmithKline Pharma GmbH.
Tel: + 43 1 970 75-0
at.info@gsk.com

Polska

GSK Commercial Sp. z o.o.
Tel.: + 48 (22) 576 9000

Portugal

GlaxoSmithKline, Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România

GlaxoSmithKline (GSK) SRL
Tel: +40 (0)21 3028 208

Slovenija

GlaxoSmithKline d.o.o.
Tel: + 386 (0) 1 280 25 00
medical.x.si@gsk.com

Slovenská republika

GlaxoSmithKline Slovakia s.r.o.
Tel: + 421 (0)2 48 26 11 11
repcia.sk@gsk.com

Suomi/Finland

GlaxoSmithKline Oy
Puh/Tel: + 358 10 30 30 30
Finland.tuoteinfo@gsk.com

Sverige

GlaxoSmithKline AB

Τηλ: + 357 22 39 70 00

Latvija

GlaxoSmithKline Latvia SIA

Tel: + 371 67312687

lv-epasts@gsk.com

Tel: + 46 (0)8 638 93 00

info.produkt@gsk.com

United Kingdom

GlaxoSmithKline UK

Tel: + 44 (0)808 100 9997

customercontactuk@gsk.com

Lietuva

GlaxoSmithKline Lietuva UAB

Tel: +370 5 264 90 00

info.lt@gsk.com

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.emea.europa.eu/>.

The following information is intended for medical or healthcare professionals only:

Cervarix should be administered as soon as possible after being removed from the refrigerator. However, stability data generated indicate that Cervarix presented in monodose containers remains stable and can be administered in case it has been stored outside the refrigerator up to three days at temperatures between 8°C and 25°C or up to one day at temperatures between 25°C and 37°C.

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.

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

Cervarix suspension for injection, multidose

Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

Read all of this leaflet carefully before you start receiving this vaccine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Cervarix is and what it is used for
2. Before you receive Cervarix
3. How Cervarix is given
4. Possible side effects
5. How to store Cervarix
6. Further information

1. WHAT CERVARIX IS AND WHAT IT IS USED FOR

Cervarix is a vaccine intended to protect females against the diseases caused by infection with Human Papillomavirus (HPV) types 16 and 18.

These diseases include:

- cervical cancer (cancer of the cervix i.e. lower part of the uterus or womb),
- precancerous cervical lesions (changes in cells of the cervix that have a risk of turning into cancer).

Cervarix will not protect against all types of Human Papillomavirus. HPV types 16 and 18 are responsible for approximately 70% of cervical cancer cases.

When a female is vaccinated with Cervarix, the immune system (the body's natural defence system) will make antibodies against HPV types 16 and 18. In clinical trials Cervarix has been shown to prevent HPV types 16 and 18 related diseases in women 15-25 years of age. Cervarix also stimulates production of antibodies in females 10-14 years of age.

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

Cervarix is not used to treat HPV related diseases already present at the time of vaccination.

Cervarix should be used in accordance with official guidelines.

2. BEFORE YOU RECEIVE CERVARIX

Cervarix should not be given if
the person to be vaccinated:

- is allergic (hypersensitive) to any of the active substances or any of the other ingredients of Cervarix. The active substances and other ingredients of Cervarix are listed at the end of the leaflet (see section 6). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

- has a severe infection with a high temperature. It might be necessary to postpone the vaccination until recovery. A minor infection such as a cold should not be a problem, but talk to the doctor first.

Take special care with Cervarix

You should tell the doctor if the person to be vaccinated:

- has a bleeding problem or bruises easily.
- has any disease which reduces her resistance to infection such as HIV infection

As with all vaccines, Cervarix may not fully protect all people who are vaccinated.

Cervarix does not protect people from diseases caused by infection with HPV types 16 or 18 if they are already infected with Human Papillomavirus type 16 or 18 at the time of vaccination.

Although vaccination may protect you against cervical cancer, it is not a substitute for regular cervical screening. You should continue to follow your doctor's advice on cervical smear/Pap test (test to screen for changes in cells of the cervix caused by an HPV infection) and preventative and protective measures.

As Cervarix will not protect against all types of Human Papillomavirus, appropriate precautions against exposure to HPV and sexually transmitted diseases should continue to be used.

Cervarix will not protect against other diseases that are not caused by Human Papillomavirus.

The duration of protection after vaccination is currently unknown. In clinical trials, sustained protection has been observed in females aged 15 to 25 years for up to 6.4 years after the first dose. The need for booster dose(s) has not been investigated.

Using other medicines

Cervarix can be given with a combined booster vaccine containing diphtheria (d), tetanus (T) and pertussis [acellular] (pa) with or without inactivated poliomyelitis (IPV), (dTpa, dTpa -IPV vaccines), at a separate injection site (another part of your body, e.g. the other arm) during the same visit.

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

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

Please tell the doctor if the person to be vaccinated is taking or has recently taken any other medicines, including medicines obtained without a prescription or has recently received any other vaccine.

Pregnancy and breast-feeding

There are insufficient data concerning the use of Cervarix during pregnancy. If pregnancy occurs during the course of vaccination your doctor should be consulted. It is recommended to postpone vaccination until after completion of the pregnancy.

Ask your doctor for advice about breast-feeding before receiving Cervarix.

Driving and using machines

There is no information on the effect of Cervarix on your ability to drive or use machinery.

3. HOW CERVARIX IS GIVEN

The doctor or nurse will give Cervarix as an injection into the muscle of the upper arm.

Cervarix is intended for females from 10 years of age onwards. A total of three injections will be administered by your doctor or nurse according to the following schedule:

First injection: at chosen date
Second injection: 1 month after first injection
Third injection: 6 months after first injection

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

When Cervarix is given for the first dose, it is recommended that Cervarix (and not another vaccine against HPV) be given for the complete 3-dose vaccination course.

The vaccine should never be given into a vein.

If you forget a return visit for Cervarix:

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

If you do not finish the complete vaccination course of three injections, you may not get the best response and protection from the vaccination.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cervarix can cause side effects, although not everybody gets them.

Side effects that occurred during clinical trials with Cervarix were as follows:

- ◆ Very common (side effects which may occur in more than 1 per 10 doses of vaccine):
 - pain or discomfort at the injection site
 - redness or swelling at the injection site
 - headache
 - aching muscles, muscle tenderness or weakness (not caused by exercise)
 - tiredness

- ◆ Common (side effects which may occur in less than 1 per 10 but more than 1 per 100 doses of vaccine):
 - gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain
 - itching, red skin rash, hives (urticaria)
 - joint pain
 - fever ($\geq 38^{\circ}\text{C}$)

- ◆ Uncommon (side effects which may occur in less than 1 per 100 but more than 1 per 1,000 doses of vaccine):
 - upper respiratory tract infection (infection of the nose, throat or trachea)
 - dizziness
 - other injection site reactions such as hard lump, tingling or numbness.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CERVARIX

Keep out of the reach and sight of children.

Do not use Cervarix after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Store in the original package in order to protect from light.

After first opening, immediate use is recommended. If not used immediately, the vaccine should be stored in a refrigerator (2°C – 8°C). If not used within 6 hours it should be discarded.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Cervarix contains

- The active substances are:

Human Papillomavirus ¹ type 16 L1 protein ^{2,3,4}	20 micrograms
Human Papillomavirus ¹ type 18 L1 protein ^{2,3,4}	20 micrograms

¹Human Papillomavirus = HPV

²adjuvanted by AS04 containing:

3- <i>O</i> -desacyl-4'- monophosphoryl lipid A (MPL) ³	50 micrograms
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³ adsorbed on aluminium hydroxide, hydrated (Al(OH) ₃)	0.5 milligrams Al ³⁺ in total
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⁴L1 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 the insect *Trichoplusia ni*.

- The other ingredients are sodium chloride (NaCl), sodium dihydrogen phosphate dihydrate (NaH₂PO₄·2 H₂O) and water for injections.

What Cervarix looks like and contents of the pack

Suspension for injection.

Cervarix is a turbid white suspension.

Cervarix is available in vials for 2 doses (1 ml) in packs of 1, 10 and 100.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

Luxembourg/Luxemburg

GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

България

ГлаксоСмитКлайн ЕООД
ул. Димитър Манов бл.10
София 1408
Тел. + 359 2 953 10 34

Česká republika

GlaxoSmithKline s.r.o.
Tel: + 420 2 22 00 11 11
gsk.czmail@gsk.com

Danmark

GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
info@glaxosmithkline.dk

Deutschland

GlaxoSmithKline GmbH & Co. KG
Tel: + 49 (0)89 360448701
produkt.info@gsk.com

Eesti

GlaxoSmithKline Eesti OÜ
Tel: +372 667 6900
estonia@gsk.com

Ελλάδα

GlaxoSmithKline A.E.B.E
Τηλ: + 30 210 68 82 100

España

GlaxoSmithKline, S.A.
Tel: + 34 902 202 700
es-ci@gsk.com

France

Laboratoire GlaxoSmithKline
Tél: + 33 (0) 1 39 17 84 44
diam@gsk.com

Ireland

GlaxoSmithKline (Ireland) Ltd
Tel: + 353 (0)1 4955000

Ísland

GlaxoSmithKline ehf.
Sími: +354-530 3700

Italia

GlaxoSmithKline S.p.A.
Tel:+ 39 04 59 21 81 11

GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

Magyarország

GlaxoSmithKline Kft.
Tel.: + 36-1-2255300

Malta

GlaxoSmithKline Malta
Tel: + 356 21 238131

Nederland

GlaxoSmithKline BV
Tel: + 31 (0)30 69 38 100
nlinfo@gsk.com

Norge

GlaxoSmithKline AS
Tlf: + 47 22 70 20 00
firmapost@gsk.no

Österreich

GlaxoSmithKline Pharma GmbH.
Tel: + 43 1 970 75-0
at.info@gsk.com

Polska

GSK Commercial Sp. z o.o.
Tel.: + 48 (22) 576 9000

Portugal

GlaxoSmithKline, Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România

GlaxoSmithKline (GSK) SRL
Tel: +40 (0)21 3028 208

Slovenija

GlaxoSmithKline d.o.o.
Tel: + 386 (0) 1 280 25 00
medical.x.si@gsk.com

Slovenská republika

GlaxoSmithKline Slovakia s.r.o.
Tel: + 421 (0)2 48 26 11 11
recepcia.sk@gsk.com

Suomi/Finland

GlaxoSmithKline Oy
Puh/Tel: + 358 10 30 30 30
Finland.tuoteinfo@gsk.com

Κύπρος

GlaxoSmithKline (Cyprus) Ltd
Τηλ: + 357 22 39 70 00

Sverige

GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

Latvija

GlaxoSmithKline Latvia SIA
Tel: + 371 67312687
lv-epasts@gsk.com

United Kingdom

GlaxoSmithKline UK
Tel: + 44 (0)808 100 9997
customercontactuk@gsk.com

Lietuva

GlaxoSmithKline Lietuva UAB
Tel: +370 5 264 90 00
info.lt@gsk.com

This leaflet was last approved in.

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.emea.europa.eu/>.

The following information is intended for medical or healthcare professionals only:

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.

When using a multidose vial, each 0.5 ml dose should be withdrawn using a sterile needle and syringe; precautions should be taken to avoid contamination of the contents.

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

Cervarix suspension for injection in pre-filled syringe

Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

Read all of this leaflet carefully before you start receiving this vaccine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Cervarix is and what it is used for
2. Before you receive Cervarix
3. How Cervarix is given
4. Possible side effects
5. How to store Cervarix
6. Further information

1. WHAT CERVARIX IS AND WHAT IT IS USED FOR

Cervarix is a vaccine intended to protect females against the diseases caused by infection with Human Papillomavirus (HPV) types 16 and 18.

These diseases include:

- cervical cancer (cancer of the cervix i.e. lower part of the uterus or womb),
- precancerous cervical lesions (changes in cells of the cervix that have a risk of turning into cancer).

Cervarix will not protect against all types of Human Papillomavirus. HPV types 16 and 18 are responsible for approximately 70% of cervical cancer cases.

When a female is vaccinated with Cervarix, the immune system (the body's natural defence system) will make antibodies against HPV types 16 and 18. In clinical trials Cervarix has been shown to prevent HPV types 16 and 18 related diseases in women 15-25 years of age. Cervarix also stimulates production of antibodies in females 10-14 years of age.

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

Cervarix is not used to treat HPV related diseases already present at the time of vaccination.

Cervarix should be used in accordance with official guidelines.

2. BEFORE YOU RECEIVE CERVARIX

Cervarix should not be given if
the person to be vaccinated:

- is allergic (hypersensitive) to any of the active substances or any of the other ingredients of Cervarix. The active substances and other ingredients of Cervarix are listed at the end of the leaflet (see section 6). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.
- has a severe infection with a high temperature. It might be necessary to postpone the vaccination until recovery. A minor infection such as a cold should not be a problem, but talk to the doctor first.

Take special care with Cervarix

You should tell the doctor if the person to be vaccinated:

- has a bleeding problem or bruises easily.
- has any disease which reduces her resistance to infection such as HIV infection

As with all vaccines, Cervarix may not fully protect all people who are vaccinated.

Cervarix does not protect people from diseases caused by infection with HPV types 16 or 18 if they are already infected with Human Papillomavirus type 16 or 18 at the time of vaccination.

Although vaccination may protect you against cervical cancer, it is not a substitute for regular cervical screening. You should continue to follow your doctor's advice on cervical smear/Pap test (test to screen for changes in cells of the cervix caused by an HPV infection) and preventative and protective measures.

As Cervarix will not protect against all types of Human Papillomavirus, appropriate precautions against exposure to HPV and sexually transmitted diseases should continue to be used.

Cervarix will not protect against other diseases that are not caused by Human Papillomavirus.

The duration of protection after vaccination is currently unknown. In clinical trials, sustained protection has been observed in females aged 15 to 25 years for up to 6.4 years after the first dose. The need for booster dose(s) has not been investigated.

Using other medicines

Cervarix can be given with a combined booster vaccine containing diphtheria (d), tetanus (T) and pertussis [acellular] (pa) with or without inactivated poliomyelitis (IPV), (dTpa, dTpa -IPV vaccines), at a separate injection site (another part of your body, e.g. the other arm) during the same visit.

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

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

Please tell the doctor if the person to be vaccinated is taking or has recently taken any other medicines, including medicines obtained without a prescription or has recently received any other vaccine.

Pregnancy and breast-feeding

There are insufficient data concerning the use of Cervarix during pregnancy. If pregnancy occurs during the course of vaccination your doctor should be consulted. It is recommended to postpone vaccination until after completion of the pregnancy.

Ask your doctor for advice about breast-feeding before receiving Cervarix.

Driving and using machines

There is no information on the effect of Cervarix on your ability to drive or use machinery.

3. HOW CERVARIX IS GIVEN

The doctor or nurse will give Cervarix as an injection into the muscle of the upper arm.

Cervarix is intended for females from 10 years of age onwards. A total of three injections will be administered by your doctor or nurse according to the following schedule:

First injection: at chosen date

Second injection: 1 month after first injection

Third injection: 6 months after first injection

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

When Cervarix is given for the first dose, it is recommended that Cervarix (and not another vaccine against HPV) be given for the complete 3-dose vaccination course.

The vaccine should never be given into a vein.

If you forget a return visit for Cervarix:

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

If you do not finish the complete vaccination course of three injections, you may not get the best response and protection from the vaccination.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cervarix can cause side effects, although not everybody gets them.

Side effects that occurred during clinical trials with Cervarix were as follows:

- ◆ Very common (side effects which may occur in more than 1 per 10 doses of vaccine):
 - pain or discomfort at the injection site
 - redness or swelling at the injection site
 - headache
 - aching muscles, muscle tenderness or weakness (not caused by exercise)
 - tiredness

- ◆ Common (side effects which may occur in less than 1 per 10 but more than 1 per 100 doses of vaccine):
 - gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain
 - itching, red skin rash, hives (urticaria)
 - joint pain
 - fever ($\geq 38^{\circ}\text{C}$)

- ◆ Uncommon (side effects which may occur in less than 1 per 100 but more than 1 per 1,000 doses of vaccine):
 - upper respiratory tract infection (infection of the nose, throat or trachea)
 - dizziness
 - other injection site reactions such as hard lump, tingling or numbness.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CERVARIX

Keep out of the reach and sight of children.

Do not use Cervarix after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in a refrigerator ($2^{\circ}\text{C} - 8^{\circ}\text{C}$).

Do not freeze.

Store in the original package in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Cervarix contains

- The active substances are:

Human Papillomavirus ¹ type 16 L1 protein ^{2,3,4}	20 micrograms
Human Papillomavirus ¹ type 18 L1 protein ^{2,3,4}	20 micrograms

¹Human Papillomavirus = HPV

²adjuvanted by AS04 containing:

3- <i>O</i> -desacyl-4'-monophosphoryl lipid A (MPL) ³	50 micrograms
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³ adsorbed on aluminium hydroxide, hydrated (Al(OH) ₃)	0.5 milligrams Al ³⁺ in total
---	--

⁴L1 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 the insect *Trichoplusia ni*.

- The other ingredients are sodium chloride (NaCl), sodium dihydrogen phosphate dihydrate (NaH₂PO₄·2 H₂O) and water for injections.

What Cervarix looks like and contents of the pack

Suspension for injection in pre-filled syringe.

Cervarix is a turbid white suspension.

Cervarix is available in pre-filled syringes with or without needles in packs of 1 and 10.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

Luxembourg/Luxemburg
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

България
ГлаксоСмитКлайн ЕООД
ул. Димитър Манов бл.10
София 1408

Magyarország
GlaxoSmithKline Kft.
Tel.: + 36-1-2255300

Тел. + 359 2 953 10 34

Česká republika

GlaxoSmithKline s.r.o.
Tel: + 420 2 22 00 11 11
gsk.czmail@gsk.com

Danmark

GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
info@glaxosmithkline.dk

Deutschland

GlaxoSmithKline GmbH & Co. KG
Tel: + 49 (0)89 360448701
produkt.info@gsk.com

Eesti

GlaxoSmithKline Eesti OÜ
Tel: +372 667 6900
estonia@gsk.com

Ελλάδα

GlaxoSmithKline A.E.B.E
Τηλ: + 30 210 68 82 100

España

GlaxoSmithKline, S.A.
Tel: + 34 902 202 700
es-ci@gsk.com

France

Laboratoire GlaxoSmithKline
Tél: + 33 (0) 1 39 17 84 44
diam@gsk.com

Ireland

GlaxoSmithKline (Ireland) Ltd
Tel: + 353 (0)1 4955000

Ísland

GlaxoSmithKline ehf.
Sími: +354-530 3700

Italia

GlaxoSmithKline S.p.A.
Tel:+ 39 04 59 21 81 11

Κύπρος

GlaxoSmithKline (Cyprus) Ltd
Τηλ: + 357 22 39 70 00

Latvija

Malta

GlaxoSmithKline Malta
Tel: + 356 21 238131

Nederland

GlaxoSmithKline BV
Tel: + 31 (0)30 69 38 100
ninfo@gsk.com

Norge

GlaxoSmithKline AS
Tlf: + 47 22 70 20 00
firmapost@gsk.no

Österreich

GlaxoSmithKline Pharma GmbH.
Tel: + 43 1 970 75-0
at.info@gsk.com

Polska

GSK Commercial Sp. z o.o.
Tel.: + 48 (22) 576 9000

Portugal

GlaxoSmithKline, Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România

GlaxoSmithKline (GSK) SRL
Tel: +40 (0)21 3028 208

Slovenija

GlaxoSmithKline d.o.o.
Tel: + 386 (0) 1 280 25 00
medical.x.si@gsk.com

Slovenská republika

GlaxoSmithKline Slovakia s.r.o.
Tel: + 421 (0)2 48 26 11 11
recepacia.sk@gsk.com

Suomi/Finland

GlaxoSmithKline Oy
Puh/Tel: + 358 10 30 30 30
Finland.tuoteinfo@gsk.com

Sverige

GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

United Kingdom

GlaxoSmithKline Latvia SIA
Tel: + 371 67312687
lv-epasts@gsk.com

GlaxoSmithKline UK
Tel: + 44 (0)808 100 9997
customercontactuk@gsk.com

Lietuva

GlaxoSmithKline Lietuva UAB
Tel: +370 5 264 90 00
info.lt@gsk.com

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.emea.europa.eu/>.

The following information is intended for medical or healthcare professionals only:

Cervarix should be administered as soon as possible after being removed from the refrigerator. However, stability data generated indicate that Cervarix presented in monodose containers remains stable and can be administered in case it has been stored outside the refrigerator up to three days at temperatures between 8°C and 25°C or up to one day at temperatures between 25°C and 37°C.

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

The content of the syringe 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.