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PRACTICAL EXPERIENCE FROM PATH

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Cervarix Summary of Product Characteristics

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Cervarix

▼ This medicine is monitored intensively by the CHM and MHRA

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

[1]Human Papillomavirus = HPV

[2]adjuvanted by AS04 containing:

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

[3]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$) 0.5 milligrams Al^{3+} in total

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

For 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.

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

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.

Cervarix may be administered concomitantly with a combined hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (HAB vaccine).

Administration of Cervarix at the same time as Twinrix (HAB vaccine) has shown no clinically relevant interference in the antibody response to the HPV and hepatitis A antigens. Anti-HBs geometric mean antibody titers were lower on co-administration, but the clinical significance of this observation is not known since the seroprotection rates remain unaffected. The proportion of subjects reaching anti-HBs $\geq$10mIU/ml was 98.3% for concomitant vaccination and 100% for Twinrix alone.

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 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

Clinical trials

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 (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥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 (≥38°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.

Post marketing surveillance

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

Blood and lymphatic system disorders

Lymphadenopathy

Immune system disorders

Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema

Nervous system disorders

Syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements (see section 4.4)

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

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

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**
	N	**n**	**N**	**n**	**(97.9% CI)**
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 ($NaH_2PO_4.2\ H_2O$)

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

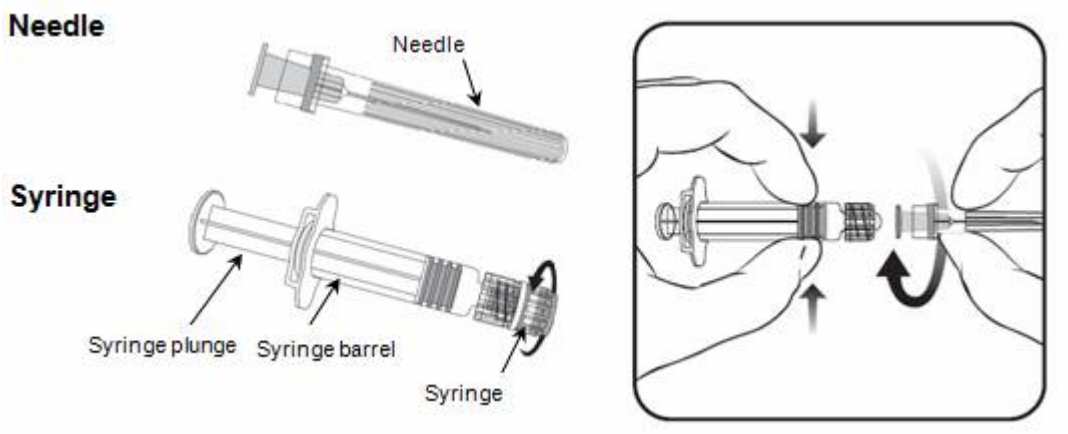
A fine white deposit with a clear colourless supernatant may be observed upon storage of the syringe. This does not constitute a sign of deterioration.

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.

<u>Instructions for administration of the vaccine presented in pre-filled syringe</u>



1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.

2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock. (see picture)

3. Remove the needle protector, which on occasion can be a little stiff.

4. Administer the vaccine.

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)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2007.

10. DATE OF REVISION OF THE TEXT

23 November 2009

11. LEGAL STATUS

POM

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