Increased Risk of Cervical Cancer in HIV Infected Women.

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Vaccines Medical Lead,
South and Southern Africa.

Namibia, 28 November 2016
This event is sponsored by GSK in the interest of advancing the scientific and educational knowledge of healthcare professionals.

GSK does not approve or recommend the use of medicines in any way other than is in the approved package inserts. For full prescribing information refer to the package insert.
I am a full time employee of GlaxoSmithKline Vaccines
AGENDA

Introduction – disease burden, overview and prevention strategies

HPV vaccines – design and the science behind

Cervarix – efficacy, duration of protection and real-world impact

Vaccine safety

Discussion
AGENDA

- Introduction – disease burden, overview and prevention strategies
- HPV vaccines – design and the science behind
- Cervarix – efficacy, duration of protection and real-world impact
- Vaccine safety
- Discussion
Burden of Cervical Cancer

Based on Globocan 2012\(^1\) estimates

- Estimated 528,000 new cases in 2012 worldwide of which 85% in less developed regions
- Eastern and Southern Africa are high risk regions with 43 and 32 cases per 100,000
- Mortality varies 18-fold between the different regions of the world, with rates ranging from less than 2 per 100,000 in Western Asia, Western Europe to more than 20 per 100,000 in Middle (22.2) and Eastern (27.6) Africa
Worldwide, every 2 minutes a woman dies of cervical cancer.¹

**Globocan 2012 worldwide data²**

- Annual incidence cervical cancer – 528,000 cases (ASR 14.0)
- Annual mortality cervical cancer – 266,000 women (ASR 6.8)

**Globocan 2012 worldwide data_Namibia²**

- Annual incidence cervical cancer – 132,000 cases (ASR 14.7)
- Annual mortality cervical cancer – 59,000 women (ASR 6.9)

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Disease Overview
HPV-infection in the cervix

1. Microlesion in the mucosa

2. Virus infects the basal cells

3. HPV follows the host cell cycle

4. Virus stays in epithelial cells, not in blood

5. Spreading of new virus particles out of reach of the immune system

HPV, human papillomavirus
Role of HPV Infection

HPV

- High Parity
- Oral contraceptives*
- Smoking
- HIV

Cervical Cancer

Coinfection With Other Sexually Transmitted Infections
- Diet
- Endogenous Hormones
- Genetic Factors

References:
HPV and HIV

- Incidence and persistence of HPV infection much higher in HIV infected women; clearance of virus is lower.
- Higher HPV viral load in HIV infected women.
- Infection with multiple HPV genotypes is more common in HIV positive women.
- HIV positive women at greater risk of lower genital tract cytological/histological abnormalities and (pre) cancers including vulvar and anal cancers.
- HIV positive women with invasive cervical cancer almost 5-10 years younger than HIV sero-negative women.

Cervical cancer and most prevalent associated HPV types

There are two main types of invasive cervical cancer:

- **Squamous cell carcinoma (~80%)**
  - Originates in the squamous epithelial cells usually found on the outer surface of the cervix\(^1,2\)
  - HPV type 16 is largely predominant (≈60%)

- **Adenocarcinoma (~5–15%)**
  - Originates in the adenomatous gland cells typically located higher in the cervix within the endocervical canal\(^1,2\)
  - More difficult to detect than squamous cell carcinoma\(^3\)
  - Incidence and mortality associated with adenocarcinoma appears to be rising\(^4\)
  - HPV type 16 and 18 contribute in more closer proportions (≈ 50%/30%)
  - Other HPV types contributor to both carcinoma are HPV-45 >33>31>52>58>35

<table>
<thead>
<tr>
<th>HPV type (relative contribution)(^5)</th>
<th>Squamous cell carcinoma</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>16+18</td>
<td>70.0%</td>
<td>82.3%</td>
</tr>
</tbody>
</table>

Preventing cervical cancer and its consequences
Twin-strategy approach

Healthy

Precancer

Cancer

Debilitation/death

Treatment

- Cancer treatment often includes removal of the womb, chemotherapy and/or radiotherapy

Twin-strategy approach

Healthy

Precancer

Cervical screening

Secondary prevention

Cancer

Debilitation/death

• Screening identifies existing precancerous lesions
• Screening allows early treatment of lesions: conization

Twin-strategy approach

Healthy

Precancer

Cancer

Debilitation/death

HPV vaccination

Primary prevention

- Screening identifies existing precancerous lesions
- Vaccination potentially prevents them occurring in the first place

HPV, human papillomavirus
Twin-strategy approach

HPV vaccination
Primary prevention

Cervical screening
Secondary prevention

- Screening identifies existing precancerous lesions
- Vaccination potentially prevents them occurring in the first place

The World Health Organization recommends a comprehensive approach to cervical cancer prevention and control including screening and vaccination³
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Discussion
Cervarix composition
GSK’s adjuvanted vaccine design principle

Bivalent HPV 16/18 AS04-adjuvanted vaccine

**AS04-containing vaccine**

**Antigens:** highly purified L1 protein from capsid assembled in VLPs

HPV-16  HPV-18

**AS04 adjuvant system**

- Aluminium salt (Al(OH)₃)
- Immunostimulant (monophosphoryl lipid A [MPL])

**Goal is to select the antigen/adjuvant system combination that can guide the immune response, delivering enhanced and sustained protection**

AS04, adjuvant system 04; Al(OH)₃, aluminium salt; MPL, monophosphoryl lipid A; HPV, human papillomavirus; VLP, virus-like particle

Adjuvant: Expected impact on vaccine immune response

- **Adjuvanted formulation**
  - Stronger/broader immune response
  - Longer-term immune response

- **Non-adjuvanted formulation**
  - Earlier immune response

Garçon N, et al. Understanding modern vaccines, perspectives in vaccinology, Vol 1, Amsterdam: Elsevier; 2011; chapter 4: p89-113
AGENDA

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Discussion
From HPV infection to cervical cancer: CIN3 is the immediate precursor of invasive cervical cancer

PROGRESSION*

Normal epithelium → HPV infection → koilocytosis → CIN1 → CIN2 → CIN3 → Invasive carcinoma

*With increasing probability of viral DNA integration

CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithelial lesion; ASCUS, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion

Phase III efficacy trial (HPV-008 PATRICIA* trial)

**women aged 15–25 years**

**Randomisation**
N = 18,644

**AS04-Adjuvanted HPV vaccine**

**Control (hepatitis A vaccine)**

**Visit**
1 2 3 4 5 6 7 8 9 10

**Month**
0 1 6 7 12 18 24 30 36 48

**End-of-study analysis**
Mean follow-up 43.7 months

**TVC-naïve**: Received ≥ 1 dose; Case counting ≥ 1 day post-Dose 1
At Month 0, had negative cytology, were HPV DNA-negative for 14 HPV types and seronegative for HPV-16 and -18

**TVC**: All women who received ≥ 1 dose, including sexually active

HPV, human papillomavirus

*PATRICIA, Papilloma TRIal against Cancer In young Adults
Multiple hrHPV infections are common in cervical neoplasia and in young women.

- **HPV-16/18 only**
- **Co-infection**
  - HPV-16/18 + other hrHPV(s)
- **No HPV 16 or 18 found (other HPV or no HPV detected)**

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1 Cuschieri K et al. J Clin Pathol 2004;57:68–72
Efficacy against lesions associated with vaccine HPV types 16 and 18

Efficacy against CIN3+ associated with HPV16/18 = 100%

HPV-16/18 only

Co-infection HPV-16/18 + other hrHPV(s)

Non-16/18 hrHPV types only

TVC-naïve: total vaccinated cohort of women who received ≥ one vaccine dose, with normal cytology, HPV DNA-negative for 14 high-risk HPV types and HPV 16/18 seronegative

Efficacy against lesions associated with non-vaccine HPV types (2)

Efficacy against CIN3+ associated with non-vaccine types excluding HPV16/18 = 81.9%

TVC-naïve: total vaccinated cohort of women who received ≥ one vaccine dose, with normal cytology, HPV DNA-negative for 14 high-risk HPV types and HPV 16/18 seronegative

Evaluating efficacy against lesions irrespective of HPV type

- HPV-16/18 only
- Co-infection HPV-16/18 + other hrHPV(s)
- No HPV 16 18 found (other HPV or no HPV detected)

Not confounded by multiple infections or limitations of HPV typing

The value of assessing efficacy irrespective of HPV type

The 2014 WHO HPV position paper\(^1\) presents efficacy data against CIN3 and CIN3+ (vaccine type and \textit{irrespective of vaccine type}) from the major Phase III HPV vaccine trials for:
- qHPV (FUTURE I & II trials)
- Cervarix™ (PATRICIA trial)

“In this paper* only data related to \textit{cervical lesions associated with any HPV type occurring in the TVC and in the TVC naïve population} are reported, as the other data are not relevant from a \textit{public health perspective}” Di Mario\(^2\)


* Systematic review and meta-analysis of the efficacy data from both available HPV vaccines
Evaluating efficacy against lesions irrespective of HPV type

Efficacy against CIN3+ irrespective of HPV type = 93.2%


TVC-naïve: total vaccinated cohort of women who received ≥ one vaccine dose, with normal cytology, HPV DNA-negative for 14 high-risk HPV types and HPV 16/18 seronegative
bHPV: 93% efficacy against CIN3+ irrespective of HPV type in the lesion

TVC-naïve cohort*

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Associated with HPV-16/18 only</th>
<th>Associated with HPV-16/18 and co-infected with a non-vaccine type</th>
<th>Associated with non-vaccine type or no HPV detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 (29.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 (31.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 (38.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HPV, human papillomavirus; TVC, total vaccinated cohort; CIN, cervical intraepithelial neoplasia;

93.2% reduction

PATRICIA trial (end-of-study$)


$Mean follow-up 43.7 months

* TVC HPV-naïve cohort: women (15–25 years) with no evidence of high-risk HPV infection at baseline, received ≥ one vaccine dose, with normal cytology, HPV DNA-negative for 14 high-risk HPV types and HPV 16/18 seronegative.
What explains the high and broad efficacy irrespective of type?
Cervarix AS04 Adjuvant System

AS04 = AL(OH)3 + MonoPhosphorylLipid A (MPL)

Cervarix is the only cervical cancer vaccine with the AS04 adjuvant system.

Papillomavirus phylogenetics: the reason behind cross-protection

HPV 18 is most closely related to HPV 45

Anogenital warts

HPV 16 is closely related to HPV 31, 33, 35, 52 and 58

Warts on hands and feet

How long could this high and broad protection last?
High and sustained immunogenicity up to 9.4 years

ELU/mL, ELISA unit/mL; GMT, geometric mean titre; HPV, human papillomavirus

Antibody levels in women (seropositive and DNA-negative) from a phase III study who cleared a natural infection before enrolment

Sustained antibody levels for HPV-31 and -45 up to 9.4 years

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>N (HPV-31)</th>
<th>N (HPV-45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 7</td>
<td>51</td>
<td>57</td>
</tr>
<tr>
<td>1 yr</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>1.5 yr</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>2.7 yr</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>6.3 yr</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>9.4 yr</td>
<td>36</td>
<td>36</td>
</tr>
</tbody>
</table>

Moscicki A et al. Presentation at IPVC 2015
Modelling of antibody level HPV-16
Predicts up to 20 and 50 yrs antibody above natural infection levels

Long-term prediction (50 years) with 95% pointwise and bootstrap confidence band using FP1 for HPV-16.

Anti-HPV-16 antibody responses predicted by the modified power-law and piece-wise model, up to 20 y EL.U/mL, ELISA units/mL; GMT, geometric mean titre; HPV, human papillomavirus; Natural infection, mean antibody titres associated with natural infection were obtained from women enrolled in a Phase III efficacy study (HPV-008, NCT00122681).

Modelling of antibody level HPV-18
Predicts up to 20 and 50 yrs Ab above natural infection levels

Long-term prediction (50 years) with 95% pointwise and bootstrap confidence band using FP1 for HPV-18.

Anti-HPV-18 antibody responses predicted by the modified power-law and piece-wise model, up to 20 y EL.U/mL, ELISA units/mL; GMT, geometric mean titre; Natural infection, mean antibody titres associated with natural infection were obtained from women enrolled in a Phase III efficacy study (HPV-008, NCT00122681)
2-dose schedule for young girls aged 9 to 14 years
Dosage Schedule

≥ 15 years

From age 15 years and above: 3-dose schedule. By IM injection.

3-dose schedule: 0, 1, 6 months. Second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose if flexibility is necessary. Necessity for a booster dose has not been established.

1. Cervarix approved package insert. GSK South Africa (Pty) Ltd. Published 08 December 2014.
Dosage Schedule 1

9 to 14 years

DOSAGE AND DIRECTIONS FOR USE (BY INTRAMUSCULAR INJECTION):

9 years to and including 14 years of age at the time of the first injection:

Administered as either a 2-dose schedule.

<table>
<thead>
<tr>
<th>Age at time of first dose</th>
<th>Immunization Schedule</th>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 to 14 years</td>
<td>2 doses: 0, 6 11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The second dose is given anytime between 5-13 months</td>
<td>If the second vaccine dose is administered before the 5th month after the first dose, a third dose should always be administered.</td>
</tr>
</tbody>
</table>

1. Cervarix approved package insert. GSK South Africa (Pty) Ltd. Published 08 December 2014.
AS04-Adjuvanted HPV vaccine in 2-dose schedule
Flexible 2-dose schedule (0, 5-13M) in 9 to 14 year old

- Non-inferiority of the 2-dose schedule in 9–14 yrs compared to 3-dose in 15-25 yrs
- Sustained immune response at least 5 years after vaccination

Romanowski et al., Hum Vac Immunoth 2014;10:5, 1–11
bHPV in HIV-positive women
HIV-positive women

**HIV-positive women**: 18-25 years, 3-dose schedule

- Immuno-safety data demonstrated the high immunogenicity of the GSK bHPV vaccine in this population:\(^1\):  

\[\text{GMT antibody levels against HPV-16 over time}^*\]

- 100% seroconversion for HPV-16 and -18
- No impact on the HIV disease’s parameters (CD4+ cell count, HIV viral load and HIV clinical stage)

* In a subset of ATP Cohort for Immunogenicity, similar curves for HPV-18

1. Denny et al., Vaccine 2013, 31; 48:5745–5753
HIV-positive women

Superior vaccine responses with bHPV among HIV-infected women\(^1\)

- bHPV induced Ab against HPV-31, -33 and 45 in >70% subjects\(^2\)

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HIV-positive population

Independent trial in HIV-positive women

12M after first dose, 3-dose regimen

bHPV vaccinees:
100% seroconversion for HPV16 and 18
>50% of vaccinated females presented Ab for HPV 31, 33, 35, 45, 56 and 58

qHPV vaccinees:
96% seroconversion for HPV16 and 73% for HPV18.
>50% of vaccinated females present Ab against non-vaccine HPV types 31, 35 and 73

The differences in seroconversion rates between vaccines were statistically significant (p < 0.05) for HPV 6,11 (qHPV), 18 and 45 (bHPV)

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Latest available data from national HPV vaccination programs_Impact
## Early impact of Cervarix immunisation programme on HPV type prevalence in Scotland

Prevalence of HPV 16 or 18 and Cross Protective types (HPV 31, 33 or 45) by the Year of Collection.

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>HPV 16 or 18</th>
<th></th>
<th>Cross-protective types (HPV 31, 33 or 45)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number positive</td>
<td>Prevalence</td>
<td>95% CI</td>
<td>Number positive</td>
</tr>
<tr>
<td>2009</td>
<td>1651</td>
<td>476</td>
<td>28.8%</td>
<td>(26.7, 31.1)%</td>
<td>215</td>
</tr>
<tr>
<td>2010</td>
<td>1053</td>
<td>333</td>
<td>31.6%</td>
<td>(28.9, 34.5)%</td>
<td>143</td>
</tr>
<tr>
<td>2011</td>
<td>1001</td>
<td>233</td>
<td>23.3%</td>
<td>(20.8, 26.0)%</td>
<td>104</td>
</tr>
<tr>
<td>2012</td>
<td>974</td>
<td>163</td>
<td>16.7%</td>
<td>(14.5, 19.2)%</td>
<td>79</td>
</tr>
</tbody>
</table>

Abbreviations: CI = Confidence interval; HPV = human papillomavirus

Update on data from Scotland
Evidence of herd immunity

- During the period 2009–2012, the prevalence of HPV 16 and 18 among unvaccinated women remained relatively stable at ≈30% but decreased to 21.2% in 2013.

- Similarly, prevalence of HPV types 31, 33, or 45 declined gradually, from 13.7% in 2010 to 9.6% in 2013.

<table>
<thead>
<tr>
<th>Study year</th>
<th>No. women</th>
<th>No. pos</th>
<th>% Pos (95% CI)</th>
<th>OR (95% CI)</th>
<th>No. pos</th>
<th>% Pos (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>1,652</td>
<td>468</td>
<td>28.3 (26.2–30.6)</td>
<td>1 (reference)</td>
<td>211</td>
<td>12.8 (11.2–14.5)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>2010</td>
<td>1,012</td>
<td>310</td>
<td>30.6 (27.9–33.5)</td>
<td>1.13 (0.95–1.34)</td>
<td>139</td>
<td>13.7 (11.8–16.0)</td>
<td>1.10 (0.87–1.38)</td>
</tr>
<tr>
<td>2011</td>
<td>557</td>
<td>164</td>
<td>29.4 (25.8–33.4)</td>
<td>1.05 (0.85–1.29)</td>
<td>71</td>
<td>12.7 (10.2–15.8)</td>
<td>0.99 (0.74–1.32)</td>
</tr>
<tr>
<td>2012</td>
<td>245</td>
<td>78</td>
<td>31.8 (26.3–37.9)</td>
<td>1.18 (0.88–1.57)</td>
<td>28</td>
<td>11.4 (8.0–16.0)</td>
<td>0.88 (0.58–1.33)</td>
</tr>
<tr>
<td>2013</td>
<td>198</td>
<td>42</td>
<td>21.2 (16.1–27.4)</td>
<td>0.67 (0.47–0.96)</td>
<td>19</td>
<td>9.6 (6.2–14.5)</td>
<td>0.71 (0.44–1.17)</td>
</tr>
</tbody>
</table>

*HPV, human papillomavirus; OR, odds ratio; pos, positive.
†HPV 31, 33, or 45.
Early impact of Cervarix immunisation programme on vaccine HPV type prevalence in Uganda

This was a comparative cross sectional study 5.5 years after a bivalent HPV 16/18 vaccination (Cervarix, GlaxoSmithKline, Belgium) pilot project in western Uganda. The age range of the participants was 15–24 years and mean age was 18.6 (SD 1.4). Vaccine-type HPV-16/18 strains were significantly less prevalent among vaccinated women compared to non-vaccinated women (0.5% vs 5.6%, p 0.006, OR 95% CI 0.08 (0.01–0.64).
History of Vaccines

History of Vaccines

AS04-Adjuvanted HPV vaccine Safety
Continuous Surveillance

• The assessment of emerging benefit-risk profile is a continuous process
• The routine pharmacovigilance is presented in the periodic safety reports
  o systematically shared with worldwide regulatory authorities according to local regulations.

Based on the last PBER/PSUR report dated January 2016

→ The safety profile of AS04-Adjuvanted HPV vaccine is adequately reflected in the current reference safety information
→ The benefit/risk balance of AS04-Adjuvanted HPV vaccine continues to be favorable
The pooled analyses for safety data from clinical trials as well as from post-marketing surveillance have not revealed any safety concerns associated with the use of AS04-Adjuvanted HPV vaccine overall or within any specific age group.

Confirmed the acceptable benefit-risk of HPV vaccination in adolescent girls and adult women.

Numerous independent analyses and review of safety data performed by independent organisation as well as recommending bodies confirm the acceptable safety profile.


1: Angelo, 2014a; Angelo, 2014b; Baril, 2015
National and Supra-national health authorities continue to reassert the positive benefit/risk profile of HPV vaccines

Take-home messages

1. HIV infection predisposes to higher incidence and persistence of HPV infections, higher HPV viral load, infection with multiple HPV genotypes and younger age of invasive cervical cancer cases.

2. GSK bHPV has demonstrated 93% efficacy irrespective of HPV type against CIN3+ in an HPV-naïve population

3. Immunogenic and acceptable benefit risk profile in HIV +ve women

4. bHPV formulated with the innovative AS04 adjuvant system induces durable immune response and protection against cervical lesions

5. Real-life data from Uganda & Scotland confirms impact and effectiveness of bHPV

6. Flexible reduced schedule 0, 5-13M for young girls aged 9 to 14 yrs

7. Confirmed acceptable benefit-risk profile

Cervarix®: Abbreviated Prescribing Information

CERVARIX. Human Papillomavirus vaccine Types 16 and 18 (Recombinant AS04 adjuvanted). Suspension for injection. Namibia Reg No. 08/30.1/0053

COMPOSITION: 1 dose (0.5 ml) contains: Human Papillomavirus type 16 L1 protein 20 µg, Human Papillomavirus type 18 L1 protein 20 µg, 3-O-desacyl-4’-monophosphoryl lipid A (MPL) 50 µg, aluminium hydroxide, hydrated 0.5 mg Al³⁺.

INDICATIONS: In females from 9 years of age onwards for the prevention of persistent infection, premalignant genital (cervical, vulvar and vaginal) lesions and cervical, vulvar and vaginal cancers caused by oncogenic Human Papillomaviruses (HPV). CONTRA-INDICATIONS: Known hypersensitivity to any component of the vaccine. Warnings and Special Precautions: Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints. Vaccination should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection should not result in the deferral of vaccination. Should not be administered intravascularly or intradermally. Should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an IM administration. A protective immune responses may not be elicited in all vaccinees. Vaccination is for primary prevention and not a substitute for regular cervical screening (secondary prevention) or for precautions against exposure to HPV and sexually transmitted diseases. Duration of protection observed for up to 9,4 years after the first dose. Not intended to prevent progression of HPV-related lesions present at the time of vaccination. Except for asymptomatic human immunodeficiency virus (HIV) infected subjects for whom limited data are available, there are no data on the use of CERVARIX in subjects with impaired immune responsiveness such as patients receiving immunosuppressive treatment. Precede vaccination by a review of the medical history and a clinical examination. Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following administration. Does not provide protection against all oncogenic HPV types. Effect on Ability to drive and use machines: No studies. INTERACTIONS: Can be given concomitantly with dTpa, IPV and the combined dTpa-IPV vaccine; HepA, HepB and the combined HepA-HepB vaccine. If to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites. There is no evidence that the use of hormonal contraceptives has an impact on the efficacy. In patients receiving immunosuppressive treatment, an adequate response may not be elicited. Should not be mixed with other medicinal products. PREGNANCY AND LACTATION: Postpone vaccination until completion of pregnancy. Should only be used during breastfeeding when the possible advantages outweigh the possible risks. DOSAGE AND DIRECTIONS FOR USE: By IM injection. The vaccination schedule depends on the age of the subjects.

<table>
<thead>
<tr>
<th>Age at the time of the first injection</th>
<th>Immunization and schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 to and including 14 years*</td>
<td>Two doses each of 0,5 ml. The second dose given between 5 and 13 months after the first dose</td>
</tr>
<tr>
<td>From 15 years and above</td>
<td>Three doses each of 0,5 ml at 0, 1, 6 months**</td>
</tr>
</tbody>
</table>

[* If the second vaccine dose is administered before the 5th month after the first dose, a third dose should always be administered.] [** If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2, 5 months after the first dose and the third dose between 5 and 12 months after the first dose.] Although the necessity for a booster dose has not been established, an anamnestic response has been observed after the administration of a challenge dose.

Use and Handling: See package insert. SIDE EFFECTS: Very common: headache, myalgia, injection site reactions including pain, redness, swelling, fatigue. Common: gastrointestinal including nausea, vomiting, diarrhea and abdominal pain, itching/pruritus, rash, urticaria, arthralgia, fever (≥38 °C). Uncommon: upper respiratory tract infection, lymphadenopathy, dizziness, other injection site reactions such as induration, local paraesthesia. Rare: allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema, syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements. Precede vaccination by a review of the medical history and a clinical examination. Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following administration. Does not provide protection against all oncogenic HPV types. MANAGEMENT OF OVERDOSAGE: None known. [GDS 23]. HCR: GlaxoSmithKline South Africa (Pty) Ltd., (Co.reg. no. 1948/030135/07), 57 Sloane Street, Bryanston 2021

Full prescribing information is available on request.
Adverse Events should be reported to GlaxoSmithKline via
telephone to +27 11 745 6000 or via e-mail to
aereporting.sna@gsk.com
Thank you.

Vaccines don’t save lives.....

Vaccination does