London, 18 October 2018
EMA/762448/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Cervarix

Common name: human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)

Procedure No. EMEA/H/C/000721/P46/090

Marketing authorisation holder (MAH): GlaxoSmithkline Biologicals SA

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Administrative information

Name of the Rapporteur	**Bart Van der Schueren**

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

The HPV-073 study report is submitted to comply with the requirements of Article 46 of the Pediatric regulation. The study aimed to evaluate the safety and immunogenicity profile of the HPV-16/18-adjuvanted vaccine in young female children 4-6 years, and whether delivery of the HPV vaccine at a paediatric age would be an alternative to the current adolescent schedule. The results of this study can be used to inform potential future HPV vaccine studies in this age range.

1.1. Steps taken for the assessment

Submission date:	11/07/2018
Start of procedure:	20/08/2018
CHMP Rapporteur's preliminary assessment report circulated on:	24/09/2018
CHMP Rapporteur's updated assessment report circulated on:	11/10/2018
CHMP opinion:	18/10/2018

2. Scientific discussion

This study is a phase III randomised, single-blind, controlled study with two parallel groups (HPV_2D and MMR_DTPa). Vaccine against HPV was administered according to a 2-dose schedule at 0,6 months in healthy female children aged 4-6 years. Vaccines against MMR and DTPa served as a control in the study wherein one dose of MMR vaccine was administered at Day 0 and one dose of DTPa vaccine at Month 6.

Independent Data Monitoring Committee (IDMC) reviewed the first interim analysis data and providedrecommendation in case a potential safety signal was identified by GSK.

Healthy female subjects between, and including, 4-6 years of age at the time of the first vaccination, who received four doses of DTP containing vaccine (i.e., three doses in the first year of life and a fourth dose in the second year of life) as well as first dose of MMR vaccine according to the local schedule applicable in the participating countries.

The duration of the study was approximately 36 months for each subject in HPV_2D group and 12 months in MMR_DTPa group.

Objectives

Co-primary

- To assess the safety, reactogenicity and occurrence of clinically relevant abnormalities in biochemistry and haematology parameters after administration of the HPV-16/18 L1 VLP AS04 vaccine according to a 2-dose schedule at 0, 6 months in 4-6 year old females, up to one month after the last dose (Month 7).

- To evaluate the immunogenicity (as determined by enzyme-linked immunosorbent assay [ELISA]) of the HPV-16/18 L1 VLP AS04 vaccine administered according to a 2-dose schedule at 0, 6 months in 4-6 year old females, one month after the last dose (Month 7).

Secondary

Immunogenicity

- To assess the immune responses to the HPV-16/18 L1 VLP AS04 vaccine as determined by ELISA on Day 0 and at Months 7, 12, 18, 24 and 36.
- To assess the immunogenicity of the measles, mumps and rubella (MMR) vaccine.
- To assess the immunogenicity of the diphtheria-tetanus-acellular pertussis (DTPa) vaccine.

Safety/Compliance

- To assess the safety of the HPV-16/18 L1 VLP AS04 vaccine throughout the study period.
- To evaluate compliance with completion of vaccination in both study groups.

The tertiary objective and results from additional tertiary objective are provided in the body of the report.

Co-Primary endpoints:

Safety

- The occurrence and intensity of solicited local adverse events (AEs) during the 7-day period (Days 0-6) following each vaccination.
- The occurrence, intensity and relationship to vaccination of solicited general AEs during the 7-day period (Days 0-6) following each vaccination.
- The occurrence, intensity and relationship to vaccination of unsolicited AEs during the 43-day period(Days 0-42) following Day 0 vaccination.
- The occurrence, intensity and relationship to vaccination of unsolicited AEs during the 30-day period(Days 0-29) following Month 6 vaccination.
- The occurrence of clinically relevant abnormalities in biochemical and haematological parameters 43days post Day 0 vaccination and 30 days post Month 6 vaccination.
- The occurrence of Serious Adverse Events (SAEs) up to Month 7.
- The occurrence of AEs and SAEs leading to withdrawal up to Month 7.
- The occurrence of potential Immune-Mediated Diseases (pIMDs) and other Medically Significant

  Conditions (MSCs), regardless of causal relationship to vaccination and intensity up to Month 7.

Immunogenicity

- Anti-HPV-16/18 seroconversion rates and antibody titres as determined by ELISA one month after the last dose (at Month 7).

Secondary endpoints:

Immunogenicity

- Anti-HPV-16/18 seroconversion rates and antibody titres as determined by ELISA on Day 0 and at Months 7 and 12 in the MMR_DTPa group as well as on Day 0 and at Months 7, 12, 18, 24 and 36 in the HPV_2D group.
- Anti-measles, mumps and rubella seropositivity rates and antibody titres on Days 0 & 42.
- Seroprotection rates to diphtheria (D) and tetanus (T) antigens at Month 7.

Safety/Compliance

- The occurrence of pIMDs up to Month 12 in both study groups.
- The occurrence of MSCs up to Month 12 in both study groups.
- The occurrence of SAEs up to Month 12 in both study groups.
- The occurrence of SAEs related to the investigational products or any fatal SAE throughout the study period (from Day 0 to Month 12 in the MMR_DTPa group and from Day 0 to Month 36 in theHPV_2D group).
- The occurrence of AEs/SAEs leading to withdrawal throughout the study period (from Day 0 to Month 12 in the MMR_DTPa group and from Day 0 to Month 36 in the HPV_2D group).
- Concomitant medication administered during the 43-day period (Days 0-42) following vaccination on Day 0 in both groups.
- Concomitant medication administered during the 30-day period (Days 0-29) following vaccination at Month 6 in both groups.
- The percentage of subjects completing the vaccination schedule.
- The occurrence, intensity and relationship to vaccination solicited fever, measles/rubella-like rash, parotid gland swelling and signs of meningism including febrile convulsion during the 43-day period(Days 0-42) following vaccination on Day 0 in the MMR_DTPa group.

Study population

Healthy female subjects between, and including, 4-6 years of age at the time of the first vaccination, who received four doses of DTP containing vaccine (i.e., three doses in the first year of life and a fourth dose in the second year of life) as well as first dose of MMR vaccine according to the local schedule applicable in the participating countries.

Study population (Total vaccinated cohort)			
Number of subjects	**HPV_2D**	**MMR_DTPa**	**Total**
Planned, N	75	75	150
Randomised, N (Total Vaccinated Cohort)	74	74	148
Completed, n (%)	73 (98.6)	71 (95.9)	144 (97.3)
Demographics	**HPV_2D**	**MMR_DTPa**	**Total**
N (Total Vaccinated Cohort)	74	74	148
Females: Males	74:.0	74:.0	148:.0
Mean Age, years (SD)	4.3 (0.5)	4.4 (0.5)	4.3 (0.5)
Median Age, years (minimum, maximum)	4 (4, 6)	4 (4, 6)	4 (4, 6)
African Heritage / African American, n (%)	4 (5.4)	2 (2.7)	6 (4.1)
White - Caucasian / European Heritage, n (%)	2 (2.7)	4 (5.4)	6 (4.1)
Other, n (%)	68 (91.9)	68 (91.9)	136 (91.9)
HPV_2D = Females aged 4-6 years who received two doses of HPV-16/18 vaccine at Day 0 and Month 6 MMR_DTPa = Females aged 4-6 years who received MMR vaccine at Day 0 and DTPa vaccine at Month 6 Other includes mixed race, Mestizo, Hispanic/Mexican and Indigenous N = total number of subjects; n (%) = number (percentage of subjects in a given category) SD = standard deviation; Mean Age = Age calculated from date of birth to first study vaccination			

The primary analysis was based on the according-to-protocol (ATP) cohort for analysis of immunogenicity. A second analysis based on the total vaccinated cohort (TVC) was performed to complement the ATP analysis.

Discussion on the rationale of the design of this study.

The primary vaccination course of GSK Biologicals' HPV vaccine consists of three doses at 0, 1, 6 months. It has been demonstrated that the HPV-16/18 vaccine induces a high and sustained immune response up to 9.4 years after vaccination in female subjects aged 15-25 years [Naud, 2014]. The sustained high immune response is associated with protection from HPV infection as well as protection against cervical precancerous lesions associated with HPV-16/18 infection (Studies HPV-001/007/023) [Harper, 2006; GlaxoSmithKline Vaccine HPV-007 Study Group, 2009; Roteli-Martins, 2012; Naud, 2014]. Statistical models predict that the antibody response will remain above the level induced by natural infection for at least 20 years [David, 2009]. In pre-teen/adolescent girls (aged 10-14 years), the HPV-16/18 vaccine elicited approximately 2-fold higher serum anti-HPV-16/18 antibody levels than in young adult women (aged 15-25 years) [Pedersen, 2007]. The augmented immune response in pre-teen/adolescent girls has been shown to be sustained for at least 48 months [Petäjä, 2011].

On the other hand, administration of GSK Biologicals' HPV vaccine according to an alternative 2-dose schedule at 0, 6 months in adolescent females has also been shown to be highly immunogenic [Romanowski, 2011]. The results from the GSK Biologicals' study HPV-048 showed that up to Month 48 the HPV vaccine administered on a 2-dose schedule at 0, 6 months in pre-teen/adolescent girls (aged 9-14 years) was non-inferior to the 3-dose standard schedule in females 15-25 years of age, the age group in which vaccine efficacy has been demonstrated [Romanowski, 2014]. Of importance, the kinetics of serum antibody responses in the preteen/adolescent population receiving 2 doses of the HPV-16/18 vaccine within a 6-month period are similar to those observed in young adult women who receive the standard 3-dose schedule within 6 months, suggesting that long lasting protection can be expected. Based on the high immunogenicity of the HPV vaccine in young adolescents, it is anticipated that the vaccine administered according to a 2-dose schedule at 0, 6 months in children of pre-school age could induce a similarly high and sustained immune response.

The current study was originally designed to demonstrate that the immune response induced by 2 doses of HPV vaccine administered according to a two dose schedule at Months 0 and 6 in 4-6 years old female subjects is non-inferior to three doses of HPV vaccine administered at Months 0, 1 and 6 in 15-25 years old female subjects, and that the co-administration of the HPV vaccine with MMR and DTPa vaccines (routinely recommended for children in the 4-6 years age range) would not lead to an interference in immune response to DTPa, MMR and HPV vaccine antigens. Since the start of the study, 2-dose schedules for HPV vaccination of adolescents have been approved in many countries.

Given the increasing success of adolescent immunisation programmes, the medical need for paediatric HPV vaccination (below 9 years of age) has become less clear. In addition, the recruitment of the study population of eligible 4-6 years old subjects has been very difficult due to the measles vaccination campaigns in several countries related to the Pan American Health Organisation (PAHO)/ World Health Organisation (WHO)-led measles elimination strategy. The current study therefore descriptively evaluated the immunogenicity and safety of GSK Biologicals' HPV-16/18 vaccine when administered according to a 2-dose schedule in 4-6 years old female subjects. Vaccines against measles, mumps and rubella (MMR) and against diphtheria-tetanus- pertussis (DTPa) served as a control in the study.

Safety results

Solicited adverse events: During the 7-day post-vaccination period, overall/dose incidence of at least one solicited symptom was 73.3% in the HPV_2D group and 60.7% in the control (MMR_DTPa) group.

- The overall incidence of solicited local symptoms was 63.7% in HPV_2D group and 40.0% in MMR_DTPa group. The most frequently reported local solicited symptom was pain at injection site, with an incidence of 60.3% of HPV doses in 73.0% of subjects, 20.3% after MMR vaccination and 50.7% after DTPa vaccination. Grade 3 solicited local symptoms after HPV-16/18 vaccination included injection site pain (2.7% of HPV doses in 5.4% of subjects), swelling (2.7% of HPV doses in 5.4% of subjects) and redness (0.7% of HPV doses in 1.4% of subjects). Grade 3 solicited local symptoms after DTPa vaccination included injection site swelling (9.9%), redness (5.6%) and pain (1.4%). No Grade 3 solicited local symptoms reported after MMR vaccination.
- The overall incidence of solicited general symptoms was 47.3% in HPV_2D group and 46.2% in MMR_DTPa group. The most frequent solicited general symptom after HPV-16/18 vaccination was irritability/fussiness (21.2% of HPV doses in 29.7% of subjects). The most frequently reported solicited general symptom was headache (25.7%) after MMR vaccination and irritability/fussiness (23.9%) after DTPa vaccination. Grade 3 solicited general symptoms reported after HPV-16/18 vaccination included drowsiness (2.1% of HPV doses in 4.1% of subjects), fever (0.7% of HPV doses in 1.4% of subjects), irritability/fussiness (0.7% of HPV doses in 1.4% of subjects) and loss of appetite (0.7% of HPV doses in 1.4% of subjects). Grade 3 solicited general symptoms reported after DTPa vaccination included loss of appetite (1.4%). No Grade 3 solicited general symptoms reported after MMR vaccination.

Unsolicited adverse events: Overall 64.9% of subjects in the HPV_2D group reported at least one unsolicited AE. In the control (MMR_DTPa) group, 54.1% of subjects reported at least one unsolicited AE after the MMR vaccination and 18.3% of girls reported at least one unsolicited AE after the DTPa vaccination. In both groups, the most frequently reported unsolicited AE was nasopharyngitis (in 32.4% vs. 36.5% of girls in the HPV_2D and the control (MMR_DTPa) group, respectively).

Serious adverse events (SAEs): A total of 3 SAEs were reported by 2 subjects (in the MMR_DTPa group) till Month 7, and 4 SAEs were reported by 3 subjects till Month 12 (3 SAEs were reported by 2 subjects in the MMR_DTPa group and one SAE was reported by one subject in the HPV_2D group). The SAEs were not considered to be causally related to vaccination. No fatal SAE was reported.

Withdrawal due to adverse events (AEs)/serious adverse events (SAEs): None of the subjects were withdrawn due to AEs/SAEs. Medically significant conditions (MSCs): MSCs were reported by 38 (51.4%) subjects in the HPV_2D group and 29 (39.2%) subjects in the MMR_DTPa group till Month 12.

Potential Immune-Mediated Diseases (pIMDs): None was reported till Month 12.

Clinical laboratory evaluations: In both groups, most of the subjects with haematological and biochemical parameters within the normal ranges at study entry remained as such after each vaccine dose.

Immunogenicity results

- Following 2-dose vaccination (Month 0, 6) of HPV-16/18, seroconversion rates for anti-HPV-16 and anti-HPV-18 were 100% at Month 7 and seropositivity rates remained 100% up to Month 36.
- The GMCs for both anti-HPV-16 and anti-HPV-18 antibodies peaked at Month 7 (20080.0 EU/mL for anti-HPV-16 antibody and 10621.8 EU/mL for anti-HPV-18 antibody) and then gradually declined until Month 18, after which a plateau level was reached until Month 36. Seropositive rates for measles, mumps and rubella after 43 days of MMR vaccination were 100%, 98.3% and 100%, respectively. The GMCs were 2512.3 IU/mL for anti-measles antibody, 7001.1 IU/mL for anti-mumps antibody and 124.2 IU/mL for anti-rubella antibody. Seroprotection rates for diphtheria and tetanus were both 100%, 30 days after DTPa vaccination.

Table 28 **Number and percentage of subjects with an anti-HPV-16 antibody concentration equal to or above 19 EU/mL and GMCs in subjects seronegative at pre-dose 1 (ATP cohort for immunogenicity - adapted for each timepoint)**

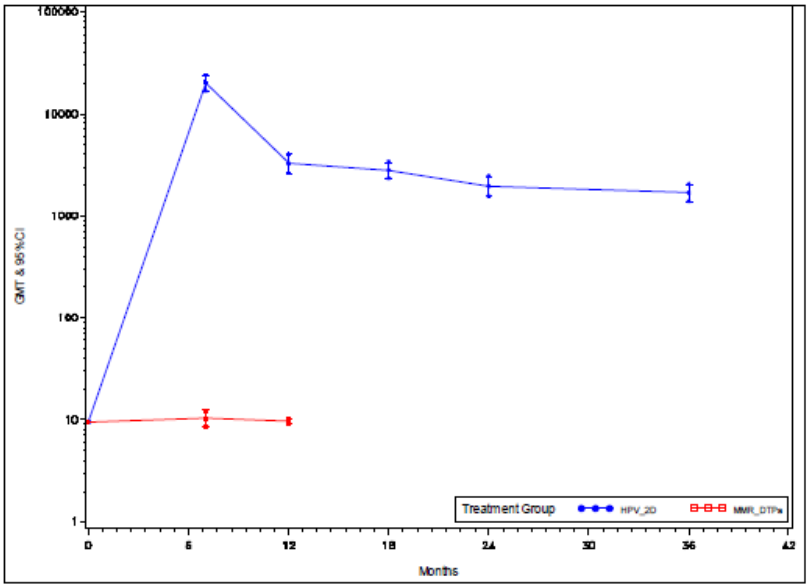
				≥ 19 EU/mL				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-HPV-16 antibody	HPV_2D	PII(M7)	64	64	100	94.4	100	20080.0	16831.8	23954.9
		PII(M12)	65	65	100	94.5	100	3246.5	2617.4	4026.8
		PII(M18)	66	66	100	94.6	100	2800.5	2325.8	3372.0
		PII(M24)	67	67	100	94.6	100	1951.9	1553.7	2452.2
		PII(M36)	67	67	100	94.6	100	1680.6	1384.2	2040.4
	MMR_DTPa	PII(M7)	43	1	2.3	0.1	12.3	10.4	8.7	12.5
		PII(M12)	48	1	2.1	0.1	11.1	9.7	9.3	10.2

HPV_2D = females aged 4-6 years who received two doses of HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month 6
MMR_DTPa = females aged 4-6 years who received MMR vaccine at Day 0 and DTPa vaccine at Month 6
GMC = geometric mean antibody concentration
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M7) = 1 month post dose 2
PII(M12) = 6 months post dose 2
PII(M18) = 12 months post dose 2
PII(M24) = 18 months post dose 2
PII(M36) = 30 months post dose 2

Table 29 **Number and percentage of subjects with an anti-HPV-18 antibody concentration equal to or above 18 EU/mL and GMCs in subjects seronegative at pre-dose 1 (ATP cohort for immunogenicity - adapted for each timepoint)**

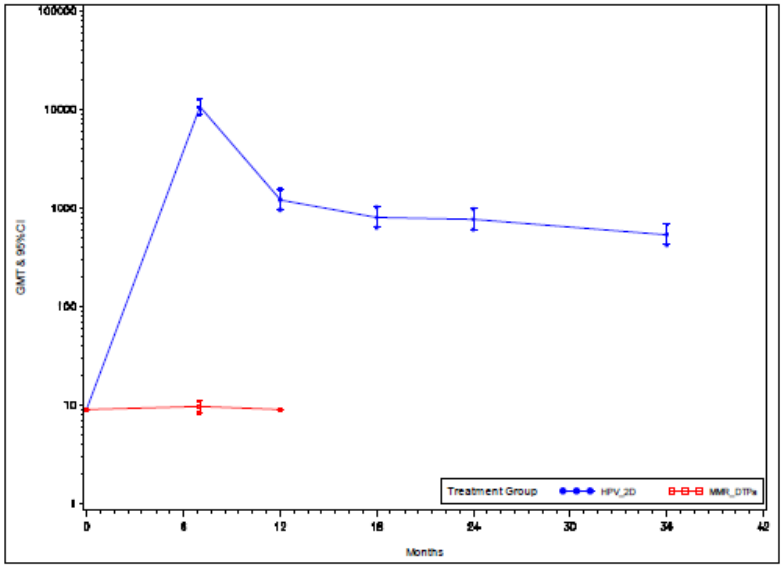
				≥ 18 EU/mL				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-HPV-18 antibody	HPV_2D	PII(M7)	62	62	100	94.2	100	10621.8	8865.3	12726.3
		PII(M12)	63	63	100	94.3	100	1216.6	953.1	1553.0
		PII(M18)	64	64	100	94.4	100	802.9	632.4	1019.5
		PII(M24)	65	65	100	94.5	100	766.6	603.3	974.2
		PII(M36)	65	65	100	94.5	100	536.4	420.6	684.0
	MMR_DTPa	PII(M7)	44	1	2.3	0.1	12.0	9.6	8.4	11.1
		PII(M12)	49	0	0.0	0.0	7.3	9.0	9.0	9.0

Figure 2 **Kinetics for anti-HPV-16 antibodies in subjects seronegative at pre-dose 1 (ATP cohort for immunogenicity - adapted for each timepoint**



HPV_2D = females aged 4-6 years who received two doses of HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month 6
MMR_DTPa = females aged 4-6 years who received MMR vaccine at Day 0 and DTPa vaccine at Month 6
GMC = geometric mean antibody concentration
The assay cut-off is 19 EU/mL

Figure 3 **Kinetics for anti-HPV-18 antibodies in subjects seronegative at pre-dose 1 (ATP cohort for immunogenicity - adapted for each timepoint**



HPV_2D = females aged 4-6 years who received two doses of HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month
MMR_DTPa = females aged 4-6 years who received MMR vaccine at Day 0 and DTPa vaccine at Month 6
GMC = geometric mean antibody concentration
The assay cut-off is 18 EU/mL

Conclusion of the MAH:

In this phase III, controlled, randomized, single-blind, multicenter study, evaluating the safety and immunogenicity of HPV-16/18 vaccine given to 4-6 year-old female subjects as a 2-dose schedule (Month 0, 6), compared to the control group receiving sequentially MMR (Month 0) and DTPa (Month 6) vaccines:

- The safety profile of the HPV-16/18 vaccine was acceptable.
- Seroconversion rates were 100% for both HPV-16 and HPV-18 one month after completion of the 2-dose HPV vaccination (i.e. Month 7). Antibody response peaked at Month 7 and persisted up to Month 36.

The MAH does not consider use of the current study data for changing the age indication.

3. CHMP overall conclusion and recommendation

The design and the rationales were discussed by the MAH.

The results in the population studied of girls aged 4 to 6 years support an acceptable safety profile and a correct antibody response that is comparable to the results seen in the 9 to 14 years of age. Of importance, the kinetics of serum antibody responses in the preteen/adolescent population receiving 2 doses of the HPV-16/18 vaccine within a 6-month period are similar to those observed in young adult women who receive the standard 3-dose schedule within 6 months, suggesting that long lasting protection can be expected.

The vaccine administered according to a 2-dose schedule at 0, 6 months in children of pre-school age induced a similarly high and sustained immune response seen in young adolescent girls. High seroconversion rates and GMTs reached for the 2 HPV types, which (although declining over time) were sufficiently maintained up to 36 months. AE frequencies were comparable with controls MMR and DTPa. Higher frequencies for both Grade 3 local and general solicited AEs were observed but are acceptable.

Meanwhile, vaccine efficacy results in this pre-school population are not available.

Based on the presented efficacy, immunogenicity and safety results the benefit risk balance for Cervarix remains positive. The presented data support the previously presented data. No regulatory action is considered necessary by the MAH based on the current study results.

The section 4.2 of the SmPC currently states :

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

The Rapporteur endorses the discussion, but the SmPC should be updated to reflect that clinical data are available in this new paediatric age group (very limited data, and outside the indication).

Member State 1 comment

Section 4.2 of the SmPC states:

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

This is not factually correct. It could be suggested to change this into "(very) limited data available".

Rapp response

Agreed.

☒ PAM not fulfilled (not all commitments fulfilled) and further action required:

The SmPC should be updated to reflect that clinical data are available in this new paediatric age group. The following wording is proposed in Section 4.2, with a cross-reference to a brief description of the available data to be included in section 5.1.

The safety, immunogenicity and efficacy of Cervarix in children below 9 years of age has not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.