

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CERVARIX safely and effectively. See full prescribing information for CERVARIX.

CERVARIX [Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant]

Suspension for Intramuscular Injection

Initial U.S. Approval: 2009

INDICATIONS AND USAGE

CERVARIX is a vaccine indicated for the prevention of the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and 18:

- cervical cancer,
- cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma *in situ*, and
- cervical intraepithelial neoplasia (CIN) grade 1. (1.1)

CERVARIX is approved for use in females 10 through 25 years of age.

Limitations of Use and Effectiveness (1.2)

- CERVARIX does not provide protection against disease due to all HPV types. (14.3)
- CERVARIX has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a woman has previously been exposed through sexual activity. (14.2)

DOSAGE AND ADMINISTRATION

Three doses (0.5-mL each) by intramuscular injection according to the following schedule: 0, 1, and 6 months. (2.2)

DOSAGE FORMS AND STRENGTHS

0.5-mL suspension for injection as a single-dose vial or pre-filled syringe. (3)

CONTRAINDICATIONS

Severe allergic reactions (e.g., anaphylaxis) to any component of CERVARIX. (4)

WARNINGS AND PRECAUTIONS

- Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with CERVARIX. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position. (5.1)
- Do not use the prefilled syringes in latex sensitive individuals. (5.2)

ADVERSE REACTIONS

- Most common local adverse reactions in $\geq 20\%$ of subjects were pain, redness, and swelling at the injection site. (6.1)
- Most common general adverse events in $\geq 20\%$ of subjects were fatigue, headache, myalgia, gastrointestinal symptoms, and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact

GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

DRUG INTERACTIONS

Do not mix CERVARIX with any other vaccine in the same syringe or vial. (7.1)

USE IN SPECIFIC POPULATIONS

- Safety has not been established in pregnant women. Register women who receive CERVARIX while pregnant in the pregnancy registry by calling 1-888-452-9622. (8.1)
- Immunocompromised individuals may have a reduced immune response to CERVARIX. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: XX/YEAR

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1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

3 1.1 Indications

4 CERVARIX[®] is indicated for the prevention of the following diseases caused by
5 oncogenic human papillomavirus (HPV) types 16 and 18 [see *Clinical Studies (14)*]:

- 6 • cervical cancer,
- 7 • cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma *in situ*, and
- 8 • cervical intraepithelial neoplasia (CIN) grade 1.

9 CERVARIX is approved for use in females 10 through 25 years of age.

10 1.2 Limitations of Use and Effectiveness

11 CERVARIX does not provide protection against disease due to all HPV types [see
12 *Clinical Studies (14.3)*].

13 CERVARIX has not been demonstrated to provide protection against disease from
14 vaccine and non-vaccine HPV types to which a woman has previously been exposed through
15 sexual activity [see *Clinical Studies (14.2)*].

16 Females should continue to adhere to recommended cervical cancer screening procedures
17 [see *Patient Counseling Information (17)*].

18 Vaccination with CERVARIX may not result in protection in all vaccine recipients.

19 2 DOSAGE AND ADMINISTRATION

20 2.1 Preparation for Administration

21 Shake vial or syringe well before withdrawal and use. Parenteral drug products should be
22 inspected visually for particulate matter and discoloration prior to administration, whenever
23 solution and container permit. CERVARIX also should be inspected visually for cracks in the
24 vial or syringe prior to administration. If any of these conditions exist, the vaccine should not be
25 administered. With thorough agitation, CERVARIX is a homogeneous, turbid, white suspension.
26 Do not administer if it appears otherwise.

27 2.2 Dose and Schedule

28 Immunization with CERVARIX consists of 3 doses of 0.5-mL each, by intramuscular
29 injection according to the following schedule: 0, 1, and 6 months. The preferred site of
30 administration is the deltoid region of the upper arm.

31 Do not administer this product intravenously, intradermally, or subcutaneously.

32 3 DOSAGE FORMS AND STRENGTHS

33 CERVARIX is a suspension for intramuscular injection available in 0.5-mL single-dose
34 vials and prefilled TIP-LOK[®] syringes.

35 **4 CONTRAINDICATIONS**

36 Severe allergic reactions (e.g., anaphylaxis) to any component of CERVARIX [*see*
37 *Description (11)*].

38 **5 WARNINGS AND PRECAUTIONS**

39 **5.1 Syncope**

40 Because vaccinees may develop syncope, sometimes resulting in falling with injury,
41 observation for 15 minutes after administration is recommended. Syncope, sometimes associated
42 with tonic-clonic movements and other seizure-like activity, has been reported following
43 vaccination with CERVARIX. When syncope is associated with tonic-clonic movements, the
44 activity is usually transient and typically responds to restoring cerebral perfusion by maintaining
45 a supine or Trendelenburg position.

46 **5.2 Latex**

47 The tip cap and the rubber plunger of the needleless prefilled syringes contain dry natural
48 latex rubber that may cause allergic reactions in latex sensitive individuals. The vial stopper does
49 not contain latex.

50 **5.3 Preventing and Managing Allergic Vaccine Reactions**

51 Prior to administration, the healthcare provider should review the immunization history
52 for possible vaccine hypersensitivity and previous vaccination-related adverse reactions to allow
53 an assessment of benefits and risks. Appropriate medical treatment and supervision should be
54 readily available in case of anaphylactic reactions following administration of CERVARIX.

55 **6 ADVERSE REACTIONS**

56 The most common local adverse reactions ($\geq 20\%$ of subjects) were pain, redness, and
57 swelling at the injection site.

58 The most common general adverse events ($\geq 20\%$ of subjects) were fatigue, headache,
59 myalgia, gastrointestinal symptoms, and arthralgia.

60 **6.1 Clinical Studies Experience**

61 Because clinical trials are conducted under widely varying conditions, adverse reaction
62 rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the
63 clinical trials of another vaccine, and may not reflect the rates observed in practice. There is the
64 possibility that broad use of CERVARIX could reveal adverse reactions not observed in clinical
65 trials.

66 Studies in Females 10 Through 25 Years of Age: The safety of CERVARIX was
67 evaluated by pooling data from controlled and uncontrolled clinical trials involving 23,713
68 females 10 through 25 years of age in the pre-licensure clinical development program. In these
69 studies, 12,785 females (10 through 25 years of age) received at least one dose of CERVARIX
70 and 10,928 females received at least one dose of a control [Hepatitis A Vaccine containing 360
71 EL.U. (10 through 14 years of age), Hepatitis A Vaccine containing 720 EL.U. (15 through
72 25 years of age), or Al(OH)₃ (500 mcg, 15 through 25 years of age)].

73 Data on solicited local and general adverse events were collected by subjects or parents
74 using standardized diary cards for 7 consecutive days following each vaccine dose (i.e., day of
75 vaccination and the next 6 days). Unsolicited adverse events were recorded with diary cards for
76 30 days following each vaccination (day of vaccination and 29 subsequent days). Parents and/or
77 subjects were also asked at each study visit about the occurrence of any adverse events and
78 instructed to immediately report serious adverse events throughout the study period. These
79 studies were conducted in North America, Latin America, Europe, Asia, and Australia. Overall,
80 the majority of subjects were white (59%), followed by Asian (26%), Hispanic (9%), black (3%),
81 and other racial/ethnic groups (3%).

82 *Solicited Adverse Events:* The reported frequencies of solicited local injection site
83 reactions (pain, redness, and swelling) and general adverse events (fatigue, fever, gastrointestinal
84 symptoms, headache, arthralgia, myalgia, and urticaria) within 7 days after vaccination in
85 females 10 through 25 years of age are presented in Table 1. An analysis of solicited local
86 injection site reactions by dose is presented in Table 2. Local reactions were reported more
87 frequently with CERVARIX when compared with the control groups; in $\geq 84\%$ of recipients of
88 CERVARIX, these local reactions were mild to moderate in intensity. Compared with dose 1,
89 pain was reported less frequently after doses 2 and 3 of CERVARIX, in contrast to redness and
90 swelling where there was a small increased incidence. There was no increase in the frequency of
91 general adverse events with successive doses.

92

93 **Table 1. Rates of Solicited Local Adverse Reactions and General Adverse Events in**
 94 **Females 10 Through 25 Years of Age Within 7 Days of Vaccination (Total Vaccinated**
 95 **Cohort^a)**

Adverse Reaction/Event	CERVARIX (10-25 yrs) %	HAV 720^b (15-25 yrs) %	HAV 360^c (10-14 yrs) %	Al(OH)₃ Control^d (15-25 yrs) %
Local Adverse Reaction	N = 6,431	N = 3,079	N = 1,027	N = 549
Pain	91.8	78.0	64.2	87.2
Redness	48.0	27.6	25.2	24.4
Swelling	44.1	19.8	17.3	21.3
General Adverse Event	N = 6,432	N = 3,079	N = 1,027	N = 549
Fatigue	55.0	53.7	42.3	53.6
Headache	53.4	51.3	45.2	61.4
GI ^e	27.8	27.3	24.6	32.8
Fever (≥99.5°F)	12.8	10.9	16.0	13.5
Rash	9.6	8.4	6.7	10.0
	N = 5,881	N = 3,079	N = 1,027	—
Myalgia ^f	49.1	44.9	33.1	—
Arthralgia ^f	20.8	17.9	19.9	—
Urticaria ^f	7.4	7.9	5.4	—

96 ^a Total vaccinated cohort included subjects with at least one documented dose (N).

97 ^b HAV 720 = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg Al(OH)₃].

98 ^c HAV 360 = Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 mcg of
 99 Al(OH)₃].

100 ^d Al(OH)₃ Control = control containing 500 mcg Al(OH)₃.

101 ^e GI = Gastrointestinal symptoms, including nausea, vomiting, diarrhea, and/or abdominal pain.

102 ^f Adverse events solicited in a subset of subjects.

103

104 **Table 2. Rates of Solicited Local Adverse Reactions in Females 10 Through 25 Years of Age**
 105 **by Dose Within 7 Days of Vaccination (Total Vaccinated Cohort^a)**

Adverse Reaction	CERVARIX (10-25 yrs) %			HAV 720 ^b (15-25 yrs) %			HAV 360 ^c (10-14 yrs) %			Al(OH) ₃ Control ^d (15-25 yrs) %		
	Post-Dose			Post-Dose			Post-Dose			Post-Dose		
	1	2	3	1	2	3	1	2	3	1	2	3
N	6,415	6,197	5,936	3,070	2,919	2,758	1,027	1,021	1,011	546	521	500
Pain	86.9	76.2	78.7	65.6	54.4	56.1	48.5	38.5	36.9	79.1	66.8	72.4
Pain, Grade 3 ^e	7.5	5.7	7.7	2.0	1.4	2.0	0.8	0.2	1.6	9.0	6.0	8.6
Redness	27.8	29.6	35.6	16.6	15.2	16.1	15.6	13.3	12.1	11.5	11.5	15.6
Redness, >50 mm	0.2	0.5	1.0	0.1	0.1	0.0	0.1	0.2	0.1	0.2	0.0	0.0
Swelling	22.7	25.2	32.7	10.5	9.4	10.5	9.4	8.6	7.6	10.3	10.4	12.0
Swelling, >50 mm	1.2	1.0	1.3	0.2	0.2	0.2	0.4	0.3	0.0	0.0	0.0	0.0

106 ^a Total vaccinated cohort included subjects with at least one documented dose (N).

107 ^b HAV 720 = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg Al(OH)₃].

108 ^c HAV 360 = Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 mcg of
 109 Al(OH)₃].

110 ^d Al(OH)₃ Control = control containing 500 mcg Al(OH)₃.

111 ^e Defined as spontaneously painful or pain that prevented normal daily activities.

112

113 The pattern of solicited local adverse reactions and general adverse events following
 114 administration of CERVARIX was similar between the age cohorts (10 through 14 years and 15
 115 through 25 years).

116 *Unsolicited Adverse Events:* The frequency of unsolicited adverse events that
 117 occurred within 30 days of vaccination ($\geq 1\%$ for CERVARIX and greater than any of the control
 118 groups) in females 10 through 25 years of age are presented in Table 3.

119

120 **Table 3. Rates of Unsolicited Adverse Events in Females 10 Through 25 Years of Age**
 121 **Within 30 Days of Vaccination ($\geq 1\%$ For CERVARIX and Greater Than HAV 720,**
 122 **HAV 360, or Al(OH)₃ Control) (Total Vaccinated Cohort^a)**

Adverse Event	CERVARIX % (N = 6,654)	HAV 720^b % (N = 3,186)	HAV 360^c % (N = 1,032)	Al(OH)₃ Control^d % (N = 581)
Headache	5.3	7.6	3.3	9.3
Nasopharyngitis	3.6	3.4	5.9	3.3
Influenza	3.2	5.6	1.3	1.9
Pharyngolaryngeal pain	2.9	2.7	2.2	2.2
Dizziness	2.2	2.6	1.5	3.1
Upper respiratory infection	2.0	1.3	6.7	1.5
Chlamydia infection	2.0	4.4	0.0	0.0
Dysmenorrhea	2.0	2.3	1.9	4.0
Pharyngitis	1.5	1.8	2.2	0.5
Injection site bruising	1.4	1.8	0.7	1.5
Vaginal infection	1.4	2.2	0.1	0.9
Injection site pruritus	1.3	0.5	0.6	0.2
Back pain	1.1	1.3	0.7	3.1
Urinary tract infection	1.0	1.4	0.3	1.2

- 123 ^a Total vaccinated cohort included subjects with at least one dose administered (N).
 124 ^b HAV 720 = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg Al(OH)₃].
 125 ^c HAV 360 = Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 mcg of
 126 Al(OH)₃].
 127 ^d Al(OH)₃ Control = control containing 500 mcg Al(OH)₃.

128
 129 *New Onset Autoimmune Diseases (NOADs):* The pooled safety database, which
 130 included controlled and uncontrolled trials which enrolled females 10 through 25 years of age,
 131 was searched for new medical conditions indicative of potential new onset autoimmune diseases.
 132 Overall, the incidence of potential NOADs, as well as NOADs, in the group receiving
 133 CERVARIX was 0.8% (95/12,533) and comparable to the pooled control group (0.8%,
 134 87/10,730) during the 4.3 years of follow-up (mean 3.0 years) (Table 4).

135 In the largest randomized, controlled trial (Study 2) which enrolled females 15 through
 136 25 years of age and which included active surveillance for potential NOADs, the incidence of
 137 potential NOADs and NOADs was 0.8% among subjects who received CERVARIX (78/9,319)
 138 and 0.8% among subjects who received Hepatitis A Vaccine [720 EL.U. of antigen and 500 mcg
 139 Al(OH)₃] control (77/9,325).

140

141 **Table 4. Incidence of New Medical Conditions Indicative of Potential New Onset**
 142 **Autoimmune Disease and New Onset Autoimmune Disease Throughout the Follow-up**
 143 **Period Regardless of Causality in Females 10 Through 25 Years of Age (Total Vaccinated**
 144 **Cohort^a)**

	CERVARIX (N = 12,533)	Pooled Control Group^b (N = 10,730)
	n (%)^c	n (%)^c
Total Number of Subjects With at Least One Medical Condition	95 (0.8)	87 (0.8)
Arthritis ^d	9 (0.1)	4 (0.0)
Celiac disease	2 (0.0)	5 (0.0)
Dermatomyositis	0 (0.0)	1 (0.0)
Diabetes mellitus insulin-dependent (Type 1 or unspecified)	5 (0.0)	5 (0.0)
Erythema nodosum	3 (0.0)	0 (0.0)
Hyperthyroidism ^e	14 (0.1)	15 (0.1)
Hypothyroidism ^f	30 (0.2)	28 (0.3)
Inflammatory bowel disease ^g	8 (0.1)	4 (0.0)
Multiple sclerosis	4 (0.0)	1 (0.0)
Myelitis transverse	1 (0.0)	0 (0.0)
Optic neuritis/Optic neuritis retrobulbar	3 (0.0)	1 (0.0)
Psoriasis ^h	8 (0.1)	11 (0.1)
Raynaud's phenomenon	0 (0.0)	1 (0.0)
Rheumatoid arthritis	4 (0.0)	3 (0.0)
Systemic lupus erythematosus ⁱ	2 (0.0)	3 (0.0)
Thrombocytopenia ^j	1 (0.0)	1 (0.0)
Vasculitis ^k	1 (0.0)	3 (0.0)
Vitiligo	2 (0.0)	2 (0.0)

145 ^a Total vaccinated cohort included subjects with at least one documented dose (N).
 146 ^b Pooled Control Group = Hepatitis A Vaccine control group [720 EL.U. of antigen and
 147 500 mcg Al(OH)₃], Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 mcg of
 148 Al(OH)₃], and a control containing 500 mcg Al(OH)₃.
 149 ^c n (%): number and percentage of subjects with medical condition.
 150 ^d Term includes reactive arthritis and arthritis.
 151 ^e Term includes Basedow's disease, goiter, and hyperthyroidism.
 152 ^f Term includes thyroiditis, autoimmune thyroiditis, and hypothyroidism.
 153 ^g Term includes colitis ulcerative, Crohn's disease, proctitis ulcerative, and inflammatory bowel
 154 disease.
 155 ^h Term includes psoriatic arthropathy, nail psoriasis, guttate psoriasis, and psoriasis.
 156 ⁱ Term includes systemic lupus erythematosus and cutaneous lupus erythematosus.

157 ^j Term includes idiopathic thrombocytopenic purpura and thrombocytopenia.

158 ^k Term includes leukocytoclastic vasculitis and vasculitis.

159

160 **Serious Adverse Events:** In the pooled safety database, inclusive of controlled and
161 uncontrolled studies, which enrolled females 10 through 72 years of age, 5.3% (862/16,142) of
162 subjects who received CERVARIX and 5.9% (814/13,811) of subjects who received control
163 reported at least one serious adverse event, without regard to causality, during the entire follow-
164 up period (up to 7.4 years).

165 Among females 10 through 25 years of age enrolled in these clinical studies, 6.4% of
166 subjects who received CERVARIX and 7.2% of subjects who received the control reported at
167 least one serious adverse event during the entire follow-up period (up to 7.4 years).

168 **Deaths:** In completed and ongoing studies which enrolled 57,323 females 9 through 72
169 years of age, 37 deaths were reported during the 7.4 years of follow-up: 20 in subjects who
170 received CERVARIX (0.06%, 20/33,623) and 17 in subjects who received control (0.07%,
171 17/23,700). Causes of death among subjects were consistent with those reported in adolescent
172 and adult female populations. The most common causes of death were motor vehicle accident (5
173 subjects who received CERVARIX; 5 subjects who received control) and suicide (2 subjects
174 who received CERVARIX; 5 subjects who received control), followed by neoplasm (3 subjects
175 who received CERVARIX; 2 subjects who received control), autoimmune disease (3 subjects
176 who received CERVARIX; 1 subject who received control), infectious disease (3 subjects who
177 received CERVARIX; 1 subject who received control), homicide (2 subjects who received
178 CERVARIX; 1 subject who received control), cardiovascular disorders (2 subjects who received
179 CERVARIX), and death of unknown cause (2 subjects who received control). Among females
180 10 through 25 years of age, 31 deaths were reported (0.05%, 16/29,467 of subjects who received
181 CERVARIX and 0.07%, 15/20,192 of subjects who received control).

182 **6.2 Postmarketing Experience**

183 In addition to reports in clinical trials, worldwide voluntary reports of adverse events
184 received for CERVARIX since market introduction (2007) are listed below. This list includes
185 serious events or events which have suspected causal association to CERVARIX. Because these
186 events are reported voluntarily from a population of uncertain size, it is not always possible to
187 reliably estimate their frequency or establish a causal relationship to vaccination.

188 **Blood and Lymphatic System Disorders:** Lymphadenopathy.

189 **Immune System Disorders:** Allergic reactions (including anaphylactic and
190 anaphylactoid reactions), angioedema, erythema multiforme.

191 **Nervous System Disorders:** Syncope or vasovagal responses to injection (sometimes
192 accompanied by tonic-clonic movements).

193 **7 DRUG INTERACTIONS**

194 **7.1 Concomitant Vaccine Administration**

195 There are no data to assess the concomitant use of CERVARIX with other vaccines.

196 Do not mix CERVARIX with any other vaccine in the same syringe or vial.

197 **7.2 Hormonal Contraceptives**

198 Among 7,693 subjects 15 through 25 years of age in Study 2 (CERVARIX, N = 3,821 or
199 Hepatitis A Vaccine 720 EL.U., N = 3,872) who used hormonal contraceptives for a mean of
200 2.8 years, the observed efficacy of CERVARIX was similar to that observed among subjects who
201 did not report use of hormonal contraceptives.

202 **7.3 Immunosuppressive Therapies**

203 Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents,
204 cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the
205 immune response to CERVARIX [*see Use in Specific Populations (8.6)*].

206 **8 USE IN SPECIFIC POPULATIONS**

207 **8.1 Pregnancy**

208 Pregnancy Category B

209 Reproduction studies have been performed in rats at a dose approximately 47 times the
210 human dose (on a mg/kg basis) and revealed no evidence of impaired fertility or harm to the
211 fetus due to CERVARIX. There are, however, no adequate and well-controlled studies in
212 pregnant women. Because animal reproduction studies are not always predictive of human
213 response, this drug should be used during pregnancy only if clearly needed.

214 Non-Clinical Studies: An evaluation of the effect of CERVARIX on embryo-fetal, pre-
215 and post-natal development was conducted using rats. One group of rats was administered
216 CERVARIX 30 days prior to gestation and during the period of organogenesis (gestation days 6,
217 8, 11, and 15). A second group of rats was administered saline at 30 days prior to gestation
218 followed by CERVARIX on days 6, 8, 11, and 15 of gestation. Two additional groups of rats
219 received either saline or adjuvant following the same dosing regimen. CERVARIX was
220 administered at 0.1 mL/rat/occasion (approximately 47-fold excess relative to the projected
221 human dose on a mg/kg basis) by intramuscular injection. No adverse effects on mating, fertility,
222 pregnancy, parturition, lactation, or embryo-fetal, pre- and post-natal development were
223 observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

224 Clinical Studies: Overall Outcomes: In clinical studies, pregnancy testing was
225 performed prior to each vaccine administration and vaccination was discontinued if a subject had
226 a positive pregnancy test. In all clinical trials, subjects were instructed to take precautions to
227 avoid pregnancy until 2 months after the last vaccination. During pre-licensure clinical
228 development, a total of 7,276 pregnancies were reported among 3,696 females receiving
229 CERVARIX and 3,580 females receiving a control (Hepatitis A Vaccine 360 EL.U., Hepatitis A
230 Vaccine 720 EL.U., or 500 mcg Al(OH)₃). The overall proportions of pregnancy outcomes were
231 similar between treatment groups. The majority of women gave birth to normal infants (62.2%
232 and 62.6% of recipients of CERVARIX and control, respectively). Other outcomes included
233 spontaneous abortion (11.0% and 10.8% of recipients of CERVARIX and control, respectively),
234 elective termination (5.8% and 6.1% of recipients of CERVARIX and control, respectively),

235 abnormal infant other than congenital anomaly (2.8% and 3.2% of recipients of CERVARIX and
236 control, respectively), and premature birth (2.0% and 1.7% of recipients of CERVARIX and
237 control, respectively). Other outcomes (congenital anomaly, stillbirth, ectopic pregnancy, and
238 therapeutic abortion) were reported less frequently in 0.1% to 0.8% of pregnancies in both
239 groups.

240 *Outcomes Around Time of Vaccination:* Sub-analyses were conducted to describe
241 pregnancy outcomes in 761 women [N = 396 for CERVARIX and N = 365 pooled control, HAV
242 360 EL.U., HAV 720 EL.U., and 500 mcg Al(OH)₃] who had their last menstrual period within
243 30 days prior to, or 45 days after a vaccine dose and for whom pregnancy outcome was known.
244 The majority of women gave birth to normal infants (65.2% and 69.3% of recipients of
245 CERVARIX and control, respectively). Spontaneous abortion was reported in a total of 11.7% of
246 subjects (13.6% of recipients of CERVARIX and 9.6% of control recipients) and elective
247 termination was reported in a total of 9.7% of subjects (9.9% of recipients of CERVARIX and
248 9.6% of control recipients). Abnormal infant other than congenital anomaly was reported in a
249 total of 4.9% of subjects (5.1% of recipients of CERVARIX and 4.7% of control recipients) and
250 premature birth was reported in a total of 2.5% of subjects (2.5% of both groups). Other
251 outcomes (congenital anomaly, stillbirth, ectopic pregnancy, and therapeutic abortion) were
252 reported in 0.3% to 1.8% of pregnancies among recipients of CERVARIX and in 0.3% to 1.4%
253 of pregnancies among control recipients.

254 It is not known whether the observed numerical imbalance in spontaneous abortions in
255 pregnancies which occurred around the time of vaccination is due to a vaccine-related effect.

256 Pregnancy Registry: Healthcare providers are encouraged to register pregnant women
257 who inadvertently receive CERVARIX in the GlaxoSmithKline vaccination pregnancy registry
258 by calling 1-888-452-9622.

259 **8.3 Nursing Mothers**

260 In non-clinical studies in rats, serological data suggest a transfer of anti-HPV-16 and
261 anti-HPV-18 antibodies via milk during lactation in rats. Excretion of vaccine-induced antibodies
262 in human milk has not been studied for CERVARIX. Because many drugs are excreted in human
263 milk, caution should be exercised when CERVARIX is administered to a nursing woman.

264 **8.4 Pediatric Use**

265 Safety and effectiveness in pediatric patients younger than 10 years of age have not been
266 established. The safety and effectiveness of CERVARIX have been evaluated in 1,193 subjects
267 10 through 14 years of age and 6,316 subjects 15 through 17 years of age. [*See Adverse*
268 *Reactions (6.1) and Clinical Studies (14.5).*]

269 **8.5 Geriatric Use**

270 Clinical studies of CERVARIX did not include sufficient numbers of subjects 65 years of
271 age and older to determine whether they respond differently from younger subjects. CERVARIX
272 is not approved for use in subjects 65 years of age and older.

273 **8.6 Immunocompromised Individuals**

274 The immune response to CERVARIX may be diminished in immunocompromised
275 individuals [see *Drug Interactions (7.3)*].

276 **11 DESCRIPTION**

277 CERVARIX [Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant]
278 is a non-infectious recombinant, AS04-adjuvanted vaccine that contains recombinant L1 protein,
279 the major antigenic protein of the capsid, of oncogenic HPV types 16 and 18. The L1 proteins
280 are produced in separate bioreactors using the recombinant Baculovirus expression vector system
281 in a serum-free culture media composed of chemically-defined lipids, vitamins, amino acids, and
282 mineral salts. Following replication of the L1 encoding recombinant Baculovirus in
283 *Trichoplusia ni* insect cells, the L1 protein accumulates in the cytoplasm of the cells. The L1
284 proteins are released by cell disruption and purified by a series of chromatographic and filtration
285 methods. Assembly of the L1 proteins into virus-like particles (VLPs) occurs at the end of the
286 purification process. The purified, non-infectious VLPs are then adsorbed on to aluminum (as
287 hydroxide salt). The adjuvant system, AS04, is composed of 3-*O*-desacyl-4'-monophosphoryl
288 lipid A (MPL) adsorbed on to aluminum (as hydroxide salt).

289 CERVARIX is prepared by combining the adsorbed VLPs of each HPV type together
290 with the AS04 adjuvant system in sodium chloride, sodium dihydrogen phosphate dihydrate, and
291 Water for Injection.

292 CERVARIX is a sterile suspension for intramuscular injection. Each 0.5-mL dose is
293 formulated to contain 20 mcg of HPV type 16 L1 protein, 20 mcg of HPV type 18 L1 protein,
294 50 mcg of the 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL), and 0.5 mg of aluminum
295 hydroxide. Each dose also contains 4.4 mg of sodium chloride and 0.624 mg of sodium
296 dihydrogen phosphate dihydrate. Each dose may also contain residual amounts of insect cell and
297 viral protein (<40 ng) and bacterial cell protein (<150 ng) from the manufacturing process.
298 CERVARIX does not contain a preservative.

299 **12 CLINICAL PHARMACOLOGY**

300 **12.1 Mechanism of Action**

301 Animal studies suggest that the efficacy of L1 VLP vaccines may be mediated by the
302 development of IgG neutralizing antibodies directed against HPV-L1 capsid proteins generated
303 as a result of vaccination.

304 **13 NONCLINICAL TOXICOLOGY**

305 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

306 CERVARIX has not been evaluated for its carcinogenic or mutagenic potential.
307 Vaccination of female rats with CERVARIX, at doses shown to be significantly immunogenic in
308 the rat, had no effect on fertility.

309 **14 CLINICAL STUDIES**

310 Cervical intraepithelial neoplasia (CIN) grade 2 and 3 lesions or cervical adenocarcinoma
311 *in situ* (AIS) are the immediate and necessary precursors of squamous cell carcinoma and
312 adenocarcinoma of the cervix, respectively. Their detection and removal has been shown to
313 prevent cancer. Therefore, CIN2/3 and AIS (precancerous lesions) serve as surrogate markers for
314 the prevention of cervical cancer. In clinical studies to evaluate the efficacy of CERVARIX, the
315 endpoints were cases of CIN2/3 and AIS associated with HPV-16, HPV-18, and other oncogenic
316 HPV types. Persistent infection with HPV-16 and HPV-18 that lasts for 12 months was also an
317 endpoint.

318 The efficacy of CERVARIX to prevent histopathologically-confirmed CIN2/3 or AIS
319 was assessed in 2 double-blind, randomized, controlled clinical studies that enrolled a total of
320 19,778 females 15 through 25 years of age.

321 Study 1 (HPV 001) enrolled women who were negative for oncogenic HPV DNA (HPV
322 types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) in cervical samples, seronegative
323 for HPV-16 and HPV-18 antibodies and had normal cytology. This represents a population
324 presumed “naïve” without current HPV infection at the time of vaccination and without prior
325 exposure to either HPV-16 or HPV-18. Subjects were enrolled in an extended follow-up study
326 (Study 1 extension [HPV 007]) to evaluate the long-term efficacy, immunogenicity, and safety.
327 These subjects have been followed for up to 6.4 years.

328 In Study 2 (HPV 008), women were vaccinated regardless of baseline HPV DNA status,
329 serostatus or cytology. This study reflects a population of women naïve (without current
330 infection and without prior exposure) or non-naïve (with current infection and/or with prior
331 exposure) to HPV. Before vaccination, cervical samples were assessed for oncogenic HPV DNA
332 (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and serostatus of HPV-16
333 and HPV-18 antibodies.

334 In both studies, testing for oncogenic HPV types was conducted using SPF₁₀-LiPA₂₅ PCR
335 to detect HPV DNA in archived biopsy samples.

336 **14.1 Prophylactic Efficacy Against HPV Types 16 and 18**

337 Study 2: A randomized, double-blind, controlled clinical trial was conducted in which
338 18,665 healthy females 15 through 25 years of age received CERVARIX or Hepatitis A Vaccine
339 control on a 0-, 1-, and 6-month schedule. Among subjects, 54.8% of subjects were white, 31.5%
340 Asian, 7.1% Hispanic, 3.7% black, and 2.9% were of other racial/ethnic groups.

341 In this study, women were randomized and vaccinated regardless of baseline HPV DNA
342 status, serostatus or cytology. Women with HPV-16 or HPV-18 DNA present in baseline
343 cervical samples (HPV DNA positive) at study entry were considered currently infected with that
344 specific HPV type. If HPV DNA was not detected by PCR, women were considered HPV DNA
345 negative. Additionally, cervical samples were assessed for cytologic abnormalities and serologic
346 testing was performed for anti-HPV-16 and anti-HPV-18 serum antibodies at baseline. Women
347 with anti-HPV serum antibodies present were considered to have prior exposure to HPV and
348 characterized as seropositive. Women seropositive for HPV-16 or HPV-18 but DNA negative for

349 that specific serotype were considered as having cleared a previous natural infection. Women
 350 without antibodies to HPV-16 and HPV-18 were characterized as seronegative. Before
 351 vaccination, 73.6% of subjects were naïve (without current infection [DNA negative] and
 352 without prior exposure [seronegative]) to HPV-16 and/or HPV-18.

353 Efficacy endpoints included histological evaluation of precancerous and dysplastic
 354 lesions (CIN grade 1, grade 2, or grade 3), and AIS. The mean follow-up after the first dose was
 355 approximately 39 months. Virological endpoints (HPV DNA in cervical samples detected by
 356 PCR) included 12-month persistent infection (defined as at least 2 positive specimens for the
 357 same HPV type over a minimum interval of 10 months).

358 The according to protocol (ATP) cohort for efficacy analyses for HPV-16 and/or HPV-18
 359 included all subjects who received 3 doses of vaccine, for whom efficacy endpoint measures
 360 were available and who were HPV-16 and/or HPV-18 DNA negative and seronegative at
 361 baseline and HPV-16 and/or HPV-18 DNA negative at month 6 for the HPV type considered in
 362 the analysis. Case counting for the ATP cohort started on day 1 after the third dose of vaccine.
 363 This cohort included women who had normal or low-grade cytology (cytological abnormalities
 364 including atypical squamous cells of undetermined significance [ASC-US] or low grade
 365 squamous intraepithelial lesions [LSIL]) at baseline and excluded women with high-grade
 366 cytology.

367 The total vaccinated cohort (TVC) for each efficacy analysis included all subjects who
 368 received at least one dose of the vaccine, for whom efficacy endpoint measures were available,
 369 irrespective of their HPV DNA status, cytology, and serostatus at baseline. This cohort included
 370 women with or without current HPV infection and/or prior exposure. Case counting for the TVC
 371 started on day 1 after the first dose.

372 The TVC naïve is a subset of the TVC that had normal cytology, and were HPV DNA
 373 negative for 14 oncogenic HPV types and seronegative for HPV-16 and HPV-18 at baseline.

374 CERVARIX was efficacious in the prevention of precancerous lesions or AIS associated
 375 with HPV-16 or HPV-18 (Table 5).

376

377 **Table 5. Efficacy of CERVARIX Against Histopathological Lesions Associated With**
 378 **HPV-16 or HPV-18 in Females 15 Through 25 Years of Age (According to Protocol**
 379 **Cohort^a) (Study 2)**

	CERVARIX		Control ^b		% Efficacy (96.1% CI) ^c
	N	Number of Cases	N	Number of Cases	
CIN2/3 or AIS	7,344	4	7,312	56	92.9 (79.9, 98.3)
CIN1/2/3 or AIS	7,344	8	7,312	96	91.7 (82.4, 96.7)

380 CI = Confidence Interval.

381 ^a Subjects (including women who had normal cytology, ASC-US, or LSIL at baseline) who
382 received 3 doses of vaccine and were HPV DNA negative and seronegative at baseline and
383 HPV DNA negative at month 6 for the corresponding HPV type (N). The mean follow-up was
384 approximately 35 months.
385 ^b Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg Al(OH)₃].
386 ^c The 96.1% confidence interval reflected in this final analysis results from statistical
387 adjustment for the previously conducted interim analysis.
388

389 Since CIN3 or AIS represents a more immediate precursor to cervical cancer, cases of
390 CIN3 or AIS associated with HPV-16 or HPV-18 were evaluated. In the ATP cohort,
391 CERVARIX was efficacious in the prevention of CIN3 or AIS associated with HPV-16 or
392 HPV-18 (vaccine efficacy = 80.0% [96.1% CI: 0.3, 98.1]).

393 Subjects who were already infected with one vaccine HPV type (16 or 18) prior to
394 vaccination were protected from precancerous lesions or AIS and infection caused by the other
395 vaccine HPV type.

396 Efficacy of CERVARIX against 12-month persistent infection with HPV-16 or HPV-18
397 was also evaluated. In the ATP cohort, CERVARIX reduced the incidence of 12-month
398 persistent infection with HPV-16 and/or HPV-18 by 91.4% (96.1% CI: 86.1, 95.0).

399 Immune response following natural infection does not reliably confer protection against
400 future infections. Among subjects who received 3 doses of CERVARIX and who were
401 seropositive at baseline and DNA negative for HPV-16 or HPV-18 at baseline and month 6,
402 CERVARIX reduced the incidence of 12-month persistent infection by 95.8% (96.1% CI: 72.4,
403 99.9). However, the number of cases of CIN2/3 or AIS was too few to determine efficacy against
404 histopathological endpoints in this population.

405 **Study 1 and Study 1 Extension:** In a second double-blind, randomized, controlled
406 study (Study 1), the efficacy of CERVARIX in the prevention of HPV-16 or HPV-18 incident
407 and persistent infections was compared with aluminum hydroxide control in 1,113 females 15
408 through 25 years of age. The population was naïve to current oncogenic HPV infection or prior
409 exposure to HPV-16 and HPV-18 at the time of vaccination (total cohort). A total of 776 subjects
410 were enrolled in the extended follow-up study (Study 1 Extension) to evaluate the long-term
411 efficacy, immunogenicity, and safety of CERVARIX. These subjects have been followed for up
412 to 6.4 years.

413 In Study 1 and Study 1 Extension, with up to 6.4 years of follow-up (mean 5.9 years), in
414 naïve females 15 through 25 years of age, efficacy against CIN2/3 or AIS associated with
415 HPV-16 or HPV-18 was 100% (98.67% CI: 28.4, 100). Efficacy against 12-month persistent
416 infection with HPV-16 or HPV-18 was 100% (98.67% CI: 74.4, 100). The confidence interval
417 reflected in this final analysis results from statistical adjustment for analyses previously
418 conducted.

419 **14.2 Efficacy Against HPV Types 16 and 18, Regardless of Current Infection or**
420 **Prior Exposure to HPV-16 or HPV-18**

421 Study 2: The study included women regardless of HPV DNA status (current infection)
422 and serostatus (prior exposure) to vaccine types, HPV-16 or HPV-18 at baseline. Efficacy
423 analyses included lesions arising among women regardless of baseline DNA status and
424 serostatus, including HPV infections present at first vaccination and those from infections
425 acquired after dose 1. In this population which includes naïve (without current infection and
426 prior exposure) and non-naïve women, CERVARIX was efficacious in the prevention of
427 precancerous lesions or AIS associated with HPV-16 or HPV-18 (Table 6).

428 However, among women HPV DNA positive regardless of serostatus at baseline, there
429 was no clear evidence of efficacy against precancerous lesions or AIS associated with HPV-16 or
430 HPV-18 (Table 6).

431

432 **Table 6. Efficacy of CERVARIX Against Disease Associated With HPV-16 or HPV-18 in**
 433 **Females 15 Through 25 Years of Age, Regardless of Current or Prior Exposure to Vaccine**
 434 **HPV Types (Study 2)**

	CERVARIX		Control		% Efficacy (96.1% CI) ^b
	N	Number of Cases ^a	N	Number of Cases ^a	
CIN1/2/3 or AIS					
Prophylactic Efficacy ^c	5,449	3	5,436	85	96.5 (89.0, 99.4)
HPV-16 or HPV-18 DNA Positive at Baseline ^d	641	90	592	92	--
Regardless of Current Infection or Prior Exposure to HPV-16 or HPV-18 ^e	8,667	107	8,682	240	55.5 ^f (43.2, 65.3)
CIN2/3 or AIS					
Prophylactic Efficacy ^c	5,449	1	5,436	63	98.4 (90.4, 100)
HPV-16 or HPV-18 DNA Positive at Baseline ^d	641	74	592	73	--
Regardless of Current Infection or Prior Exposure to HPV-16 or HPV-18 ^e	8,667	82	8,682	174	52.8 ^f (37.5, 64.7)
CIN3 or AIS					
Prophylactic Efficacy ^c	5,449	0	5,436	13	100 (64.7, 100)
HPV-16 or HPV-18 DNA Positive at Baseline ^d	641	41	592	38	--
Regardless of Current Infection or Prior Exposure to HPV-16 or HPV-18 ^e	8,667	43	8,682	65	33.6 ^f (-1.1, 56.9)

435 CI = Confidence Interval.

436 Table does not include disease due to non-vaccine HPV types.

437 ^a Cases = Histopathological cases associated with HPV-16 and/or HPV-18.

438 ^b The 96.1% confidence interval reflected in this final analysis results from statistical
 439 adjustment for the previously conducted interim analysis.

- 440 ^c TVC naïve: includes all vaccinated subjects (who received at least one dose of vaccine) who
441 had normal cytology, were HPV DNA negative for 14 oncogenic HPV types, and
442 seronegative for HPV-16 and HPV-18 at baseline (N). Case counting started on day 1 after the
443 first dose.
- 444 ^d TVC subset: includes all vaccinated subjects (who received at least one dose of vaccine) who
445 were HPV DNA positive for HPV-16 or HPV-18 irrespective of serostatus at baseline (N).
446 Case counting started on day 1 after the first dose.
- 447 ^e TVC: includes all vaccinated subjects (who received at least one dose of vaccine) irrespective
448 of HPV DNA status and serostatus at baseline (N). Case counting started on day 1 after the
449 first dose.
- 450 ^f Observed vaccine efficacy includes the prophylactic efficacy of CERVARIX and the impact
451 of CERVARIX on the course of infections present at first vaccination.
452

453 **14.3 Efficacy Against Cervical Disease Irrespective of HPV Type, Regardless of** 454 **Current or Prior Infection with Vaccine or Non-Vaccine HPV Types**

455 Study 2: The impact of CERVARIX against the overall burden of HPV-related cervical
456 disease results from a combination of prophylactic efficacy against, and disease contribution of,
457 HPV-16, HPV-18, and non-vaccine HPV types.

458 In the population naïve to oncogenic HPV (TVC naïve), CERVARIX reduced the overall
459 incidence of CIN1/2/3 or AIS, CIN2/3 or AIS, and CIN3 or AIS regardless of the HPV DNA
460 type in the lesion (Table 7). In the population of women naïve and non-naïve (TVC), vaccine
461 efficacy against CIN1/2/3 or AIS, CIN2/3 or AIS, and CIN3 or AIS was demonstrated in all
462 women regardless of HPV DNA type in the lesion (Table 7).
463

464 **Table 7. Efficacy of CERVARIX in Prevention of CIN or AIS Irrespective of Any HPV**
 465 **Type in Females 15 Through 25 Years of Age, Regardless of Current or Prior Infection**
 466 **with Vaccine or Non-Vaccine Types (Study 2)**

	CERVARIX		Control		% Efficacy (96.1% CI) ^a
	N	Number of Cases	N	Number of Cases	
CIN1/2/3 or AIS					
Prophylactic Efficacy ^b	5,449	106	5,436	211	50.1 (35.9, 61.4)
Irrespective of HPV DNA at Baseline ^c	8,667	451	8,682	577	21.7 (10.7, 31.4)
CIN2/3 or AIS					
Prophylactic Efficacy ^b	5,449	33	5,436	110	70.2 (54.7, 80.9)
Irrespective of HPV DNA at Baseline ^c	8,667	224	8,682	322	30.4 (16.4, 42.1)
CIN3 or AIS					
Prophylactic Efficacy ^b	5,449	3	5,436	23	87.0 (54.9, 97.7)
Irrespective of HPV DNA at Baseline ^c	8,667	77	8,682	116	33.4 (9.1, 51.5)

467 CI = Confidence Interval.

468 ^a The 96.1% confidence interval reflected in this final analysis results from statistical
 469 adjustment for the previously conducted interim analysis.

470 ^b TVC naïve: includes all vaccinated subjects (who received at least one dose of vaccine) who
 471 had normal cytology, were HPV DNA negative for 14 oncogenic HPV types (including
 472 HPV-16 and HPV-18), and seronegative for HPV-16 and HPV-18 at baseline (N). Case
 473 counting started on day 1 after the first dose.

474 ^c TVC: includes all vaccinated subjects (who received at least one dose of vaccine) irrespective
 475 of HPV DNA status and serostatus at baseline (N). Case counting started on day 1 after the
 476 first dose.

477
 478 In exploratory analyses, CERVARIX reduced definitive cervical therapy procedures
 479 (includes loop electrosurgical excision procedure [LEEP], cold-knife Cone, and laser procedures)
 480 by 24.7% (96.1% CI: 7.4, 38.9) in the TVC and by 68.8% (96.1% CI: 50.0, 81.2) in the TVC
 481 naïve.

482 To assess reductions in disease caused by non-vaccine HPV types, two analyses were
 483 conducted combining 12 non-vaccine oncogenic HPV types, including and excluding lesions in
 484 which HPV-16 or HPV-18 were also detected. In these analyses, among females who received 3
 485 doses of CERVARIX and were DNA negative for the specific HPV type at baseline and

486 month 6, CERVARIX reduced the incidence of CIN2/3 or AIS by 54.0% (96.1% CI: 34.0, 68.4)
487 and 37.4% (96.1% CI: 7.4, 58.2), respectively.

488 Post-hoc analyses, adjusted for multiplicity, were conducted to assess the impact of
489 CERVARIX on CIN2/3 or AIS due to specific non-vaccine HPV types. The ATP cohort for
490 these analyses included all subjects irrespective of serostatus who received 3 doses of
491 CERVARIX and were DNA negative for the specific HPV type at baseline and month 6. These
492 post-hoc analyses were also conducted in the TVC naïve population. In analyses including
493 lesions in which HPV-16 or HPV-18 were also detected, vaccine efficacy in prevention of
494 CIN2/3 or AIS associated with HPV-31 was 92.0% (99.7% CI: 49.0, 99.8) and 100% (99.7% CI:
495 62.3, 100), respectively. In analyses excluding lesions in which HPV-16 or HPV-18 were
496 detected, vaccine efficacy in prevention of CIN2/3 or AIS associated with HPV-31 was 89.4%
497 (99.7% CI: 29.0, 99.7) and 100% (99.7% CI: 36.3, 100), respectively.

498 **14.4 Immunogenicity**

499 The minimum anti-HPV titer that confers protective efficacy has not been determined.

500 The antibody response to HPV-16 and HPV-18 was measured using a type-specific
501 binding ELISA (developed by GlaxoSmithKline) and a pseudovirion-based neutralization assay
502 (PBNA). In a subset of subjects tested for HPV-16 and HPV-18, the ELISA has been shown to
503 correlate with the PBNA. The scales for these assays are unique to each HPV type and each
504 assay, thus, comparison between HPV types or assays is not appropriate.

505 Duration of Immune Response: The duration of immunity following a complete
506 schedule of immunization with CERVARIX has not been established. In Study 1 and Study 1
507 Extension, the immune response against HPV-16 and HPV-18 was evaluated for up to 76 months
508 post-dose 1, in females 15 through 25 years of age. Vaccine-induced geometric mean titers
509 (GMTs) for both HPV-16 and HPV-18 peaked at month 7 and thereafter reached a plateau that
510 was sustained from month 18 up to month 76. At all timepoints, >98% of subjects were
511 seropositive for both HPV-16 (≥ 8 EL.U./mL, the limit of detection) and HPV-18 (≥ 7 EL.U./mL,
512 the limit of detection) by ELISA.

513 In Study 2, GMTs for ELISA and PBNA one month post-dose 3 were measured
514 (Table 8). The ATP cohort for immunogenicity included all evaluable subjects for whom data
515 concerning immunogenicity endpoint measures were available. These included subjects for
516 whom assay results were available for antibodies against at least one vaccine type. Subjects who
517 acquired either HPV-16 or HPV-18 infection during the trial were excluded. Of subjects
518 seronegative at baseline, 99.5% were seropositive for anti-HPV-16 and anti-HPV-18 antibodies
519 at month 7 post-vaccination.

520

521 **Table 8. Summary of Anti-HPV Geometric Mean Titers (GMTs) for HPV-16 and HPV-18**
 522 **at Month 7 for Initially Seronegative Females 15 Through 25 Years of Age (According to**
 523 **Protocol Cohort for Immunogenicity^a) (Study 2)**

Antibody Assay	N	CERVARIX GMT (95% CI)	N	Control GMT (95% CI)
ELISA^b (EL.U./mL)				
Anti-HPV-16	865	9,206.5 (8,609.4, 9,845.1)	740	4.4 (4.2, 4.6)
Anti-HPV-18	930	4,741.3 (4,452.2, 5,049.1)	772	3.8 (3.6, 3.9)
PBNA^c (ED₅₀)				
Anti-HPV-16	46	27,364.8 (19,780.1, 37,857.9)	44	20.0 (20.0, 20.0)
Anti-HPV-18	46	9,052 (6,851.8, 11,960.5)	44	20.0 (20.0, 20.0)

524 ^a Subjects who received 3 doses of vaccine for whom assay results were available for at least
 525 one post-vaccination antibody measurement (N). Subjects who acquired either HPV-16 or
 526 HPV-18 infection during the study were excluded.

527 ^b Enzyme linked immunosorbent assay (assay cut-off 8 EL.U./mL for anti-HPV-16 antibody
 528 and 7 EL.U./mL for anti-HPV-18 antibody).

529 ^c Pseudovirion-based neutralization assay (assay cut-off 40 ED₅₀ for both anti-HPV-16
 530 antibody and anti-HPV-18 antibody).

531

532 **14.5 Bridging of Efficacy from Women to Adolescent Girls**

533 The immunogenicity of CERVARIX was evaluated in 2 clinical studies involving 1,193
 534 girls 10 through 14 years of age who received CERVARIX.

535 Study 3 (HPV 013) was a double-blind, randomized, controlled study in which 1,035
 536 subjects received CERVARIX and 1,032 subjects received a Hepatitis A Vaccine 360 EL.U. as
 537 the control vaccine with a subset of subjects evaluated for immunogenicity. All initially
 538 seronegative subjects in the group who received CERVARIX were seropositive after
 539 vaccination, i.e., had levels of antibody greater than the limit of detection of the assay to both
 540 HPV-16 (≥ 8 EL.U./mL) and HPV-18 (≥ 7 EL.U./mL) antigens. The GMTs for anti-HPV-16 and
 541 anti-HPV-18 antibodies in initially seronegative subjects are presented in Table 9.
 542

543 **Table 9. Geometric Mean Titers (GMTs) at Months 7 and 18 for Initially Seronegative**
 544 **Females 10 Through 14 Years of Age (According To Protocol Cohort for Immunogenicity^a)**
 545 **(Study 3)**

Age Group	Anti-HPV-16 Antibodies GMT EL.U./mL (95% CI)			Anti-HPV-18 Antibodies GMT EL.U./mL (95% CI)		
	N	Month 7	Month 18	N	Month 7	Month 18
10-14 years of age	556-619	19,882.0 (18,626.7, 21,221.9)	3,888.8 (3,605.0, 4,195.0)	562-628	8,262.0 (7,725.0, 8,836.2)	1,539.4 (1,418.8, 1,670.3)

546 ^a Subjects who received 3 doses of vaccine for whom assay results were available for at least
 547 one post-vaccination antibody measurement (N).
 548

549 In Study 4 (HPV 012), the immunogenicity of CERVARIX administered to girls 10
 550 through 14 years of age was compared to that in females 15 through 25 years of age. The
 551 immune response in girls 10 through 14 years of age measured one month post-dose 3 was non-
 552 inferior to that seen in females 15 through 25 years of age for both HPV-16 and HPV-18
 553 antigens (Table 10).
 554

555 **Table 10. Geometric Mean Titers (GMTs) and Seropositivity Rates at Month 7 for Initially**
 556 **Seronegative Females 10 Through 14 Years of Age Compared to 15 Through 25 Years of**
 557 **Age (According To Protocol Cohort for Immunogenicity^a) (Study 4)**

Antibody Assay	10-14 Years of Age			15-25 Years of Age		
	N	GMT ^b EL.U./mL (95% CI)	Seropositivity Rate ^c %	N	GMT ^b EL.U./mL (95% CI)	Seropositivity Rate ^c %
Anti-HPV-16	143	17,272.5 (15,117.9, 19,734.1)	100	118	7,438.9 (6,324.6, 8,749.6)	100
Anti-HPV-18	141	6,863.8 (5,976.3, 7,883.0)	100	116	3,070.1 (2,600.0, 3,625.4)	100

558 ^a Subjects who received 3 doses of vaccine for whom assay results were available for at least
 559 one post-vaccination antibody measurement (N).

560 ^b Non-inferiority based on the upper limit of the 2-sided 95% CI for the GMT ratio (15-25 year
 561 olds/10-14 year olds) was <2.

562 ^c Non-inferiority based on the upper limit of the 2-sided 95% CI for the difference between the
 563 seropositivity rates for 10-14 year olds and 15-25 year olds was <10%.
 564

565 Based on these immunogenicity data, the efficacy of CERVARIX is inferred in girls 10
 566 through 14 years of age.

567 **16 HOW SUPPLIED/STORAGE AND HANDLING**

568 CERVARIX is available in 0.5-mL single-dose vials and prefilled TIP-LOK syringes.

569 Single-Dose Vials
570 NDC 58160-830-11 (package of 10)
571 Single-Dose Prefilled Disposable TIP-LOK Syringes (packaged without needles)
572 NDC 58160-830-32 (package of 1)
573 NDC 58160-830-46 (package of 5)
574 Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the
575 vaccine has been frozen. Upon storage, a fine, white deposit with a clear, colorless supernatant
576 may be observed. This does not constitute a sign of deterioration.

577 **17 PATIENT COUNSELING INFORMATION**

578 Provide the Vaccine Information Statements prior to immunization. This is required by
579 the National Childhood Vaccine Injury Act of 1986 and are available free of charge at the
580 Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

581 Inform the patient, parent, or guardian:

- 582 • Vaccination does not substitute for routine cervical cancer screening. Women who receive
583 CERVARIX should continue to undergo cervical cancer screening per standard of care.
- 584 • CERVARIX does not protect against disease from HPV types to which a woman has
585 previously been exposed through sexual activity.
- 586 • Since syncope has been reported following vaccination in young females, sometimes
587 resulting in falling with injury, observation for 15 minutes after administration is
588 recommended.
- 589 • Information regarding potential benefits and risks associated with vaccination.
- 590 • Report any adverse events to their healthcare provider.
- 591 • Safety has not been established in pregnant women. CERVARIX is not recommended for use
592 in pregnant women or women planning to become pregnant during the vaccination course.
593 Register women who receive CERVARIX while pregnant in the pregnancy registry by
594 calling 1-888-452-9622.

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