

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 9 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

Single-dose prefilled syringes containing a 0.5-mL suspension for injection. (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)
- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (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. (8.1)
- Immunocompromised individuals may have a reduced immune response to CERVARIX. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: xx/xxxx

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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 oncogenic
5 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 9 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 Clinical*
12 *Studies (14.3)*].

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

16 Females should continue to adhere to recommended cervical cancer screening procedures [*see*
17 *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 syringe well before withdrawal and use. Parenteral drug products should be inspected
22 visually for particulate matter and discoloration prior to administration, whenever solution and
23 container permit. If either of these conditions exists, the vaccine should not be administered.

24 With thorough agitation, CERVARIX is a homogeneous, turbid, white suspension. Do not
25 administer if it appears otherwise.

26 Attach a sterile needle and administer intramuscularly.

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

28 2.2 Dose and Schedule

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

32 **3 DOSAGE FORMS AND STRENGTHS**

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

35 **4 CONTRAINDICATIONS**

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

38 **5 WARNINGS AND PRECAUTIONS**

39 **5.1 Syncope**

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

46 **5.2 Latex**

47 The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic
48 reactions.

49 **5.3 Preventing and Managing Allergic Vaccine Reactions**

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

54 **6 ADVERSE REACTIONS**

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

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

59 **6.1 Clinical Studies Experience**

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

65 Studies in Females 9 through 25 Years of Age

66 The safety of CERVARIX was evaluated by pooling data from controlled and uncontrolled
67 clinical trials involving 23,952 females 9 through 25 years of age in the pre-licensure clinical
68 development program. In these studies, 13,024 females (9 through 25 years of age) received at
69 least one dose of CERVARIX and 10,928 females received at least one dose of a control
70 [Hepatitis A Vaccine containing 360 EL.U. (10 through 14 years of age), Hepatitis A Vaccine
71 containing 720 EL.U. (15 through 25 years of age), or Al(OH)₃ (500 mcg, 15 through 25 years of
72 age)].

73 Data on solicited local and general adverse events were collected by subjects or parents using
74 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 (59.5%), followed by Asian (25.9%), Hispanic (8.5%), black
81 (3.4%), and other racial/ethnic groups (2.7%).

82 *Solicited Adverse Events:* The reported frequencies of solicited local injection site reactions
83 (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 9 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 $\geq 76\%$ 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 **Table 1. Rates of Solicited Local Adverse Reactions and General Adverse Events in**
 93 **Females 9 through 25 Years of Age within 7 Days of Vaccination (Total Vaccinated**
 94 **Cohort^a)**

	CERVARIX (9-25 years) %	HAV 720^b (15-25 years) %	HAV 360^c (10-14 years) %	Al(OH)₃ Control^d (15-25 years) %
Local Adverse Reaction	N = 6,669	N = 3,079	N = 1,027	N = 549
Pain	91.9	78.0	64.2	87.2
Redness	48.4	27.6	25.2	24.4
Swelling	44.3	19.8	17.3	21.3
General Adverse Event	N = 6,670	N = 3,079	N = 1,027	N = 549
Fatigue	54.6	53.7	42.3	53.6
Headache	53.4	51.3	45.2	61.4
GI ^e	27.9	27.3	24.6	32.8
Fever (≥99.5°F)	12.9	10.9	16.0	13.5
Rash	9.5	8.4	6.7	10.0
	N = 6,119	N = 3,079	N = 1,027	—
Myalgia ^f	48.8	44.9	33.1	—
Arthralgia ^f	20.7	17.9	19.9	—
Urticaria ^f	7.2	7.9	5.4	—

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

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

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

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

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

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

102 **Table 2. Rates of Solicited Local Adverse Reactions in Females 9 through 25 Years of Age**
 103 **by Dose within 7 Days of Vaccination (Total Vaccinated Cohort^a)**

	CERVARIX (9-25 years) %			HAV 720 ^b (15-25 years) %			HAV 360 ^c (10-14 years) %			Al(OH) ₃ Control ^d (15-25 years) %		
	Post-dose			Post-dose			Post-dose			Post-dose		
	1	2	3	1	2	3	1	2	3	1	2	3
N	6,653	6,428	6,168	3,070	2,919	2,758	1,027	1,021	1,011	546	521	500
Pain	87.0	76.4	78.5	65.6	54.4	56.1	48.5	38.5	36.9	79.1	66.8	72.4
Pain, Grade 3 ^e	7.5	5.6	7.7	2.0	1.4	2.0	0.8	0.2	1.6	9.0	6.0	8.6
Redness	28.4	30.1	35.7	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	22.8	25.5	32.7	10.5	9.4	10.5	9.4	8.6	7.6	10.3	10.4	12.0
Swelling, >50 mm	1.1	1.0	1.3	0.2	0.2	0.2	0.4	0.3	0.0	0.0	0.0	0.0

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

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

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

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

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

110 The pattern of solicited local adverse reactions and general adverse events following
 111 administration of CERVARIX was similar between the age cohorts (9 through 14 years and 15
 112 through 25 years).

113 *Unsolicited Adverse Events:* The frequency of unsolicited adverse events that occurred within
 114 30 days of vaccination (≥1% for CERVARIX and greater than any of the control groups) in
 115 females 9 through 25 years of age are presented in Table 3.

116 **Table 3. Rates of Unsolicited Adverse Events in Females 9 through 25 Years of Age within**
 117 **30 Days of Vaccination (≥1% For CERVARIX and Greater than HAV 720, HAV 360, or**
 118 **Al(OH)₃ Control) (Total Vaccinated Cohort^a)**

	CERVARIX	HAV 720^b	HAV 360^c	Al(OH)₃ Control^d
	%	%	%	%
	N = 6,893	N = 3,186	N = 1,032	N = 581
Headache	5.2	7.6	3.3	9.3
Nasopharyngitis	3.7	3.4	5.9	3.3
Influenza	3.1	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	1.9	4.4	0.0	0.0
Dysmenorrhea	1.9	2.3	1.9	4.0
Pharyngitis	1.4	1.8	2.2	0.5
Injection site bruising	1.4	1.8	0.7	1.5
Vaginal infection	1.3	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

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

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

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

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

124 *New Onset Autoimmune Diseases (NOADs)*: The pooled safety database, which included
 125 controlled and uncontrolled trials which enrolled females 9 through 25 years of age, was
 126 searched for new medical conditions indicative of potential new onset autoimmune diseases.
 127 Overall, the incidence of potential NOADs, as well as NOADs, in the group receiving
 128 CERVARIX was 0.8% (96/12,772) and comparable to the pooled control group (0.8%,
 129 87/10,730) during the 4.3 years of follow-up (Table 4).

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

135 **Table 4. Incidence of New Medical Conditions Indicative of Potential New Onset**
 136 **Autoimmune Disease and New Onset Autoimmune Disease throughout the Follow-up**
 137 **Period Regardless of Causality in Females 9 through 25 Years of Age (Total Vaccinated**
 138 **Cohort^a)**

	CERVARIX	Pooled Control Group^b
	N = 12,772	N = 10,730
	n (%)^c	n (%)^c
Total Number of Subjects with at Least One Medical Condition	96 (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	15 (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)

139 ^a Total vaccinated cohort included subjects with at least one documented dose (N).
 140 ^b Pooled Control Group = Hepatitis A Vaccine control group [720 EL.U. of antigen and
 141 500 mcg Al(OH)₃], Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 mcg of
 142 Al(OH)₃], and a control containing 500 mcg Al(OH)₃.
 143 ^c n (%): Number and percentage of subjects with medical condition.
 144 ^d Term includes reactive arthritis and arthritis.
 145 ^e Term includes Basedow's disease, goiter, and hyperthyroidism.
 146 ^f Term includes thyroiditis, autoimmune thyroiditis, and hypothyroidism.
 147 ^g Term includes colitis ulcerative, Crohn's disease, proctitis ulcerative, and inflammatory bowel
 148 disease.
 149 ^h Term includes psoriatic arthropathy, nail psoriasis, guttate psoriasis, and psoriasis.
 150 ⁱ Term includes systemic lupus erythematosus and cutaneous lupus erythematosus.

151 ^j Term includes idiopathic thrombocytopenic purpura and thrombocytopenia.

152 ^k Term includes leukocytoclastic vasculitis and vasculitis.

153 Serious Adverse Events

154 In the pooled safety database, inclusive of controlled and uncontrolled studies, which enrolled
155 females 9 through 72 years of age, 5.3% (864/16,381) of subjects who received CERVARIX and
156 5.9% (814/13,811) of subjects who received control reported at least one serious adverse event,
157 without regard to causality, during the entire follow-up period (up to 7.4 years).

158 Among females 9 through 25 years of age enrolled in these clinical studies, 6.3% of subjects who
159 received CERVARIX and 7.2% of subjects who received the control reported at least one serious
160 adverse event during the entire follow-up period (up to 7.4 years).

161 Deaths

162 In completed and ongoing studies which enrolled 57,323 females 9 through 72 years of age, 37
163 deaths were reported during the 7.4 years of follow-up: 20 in subjects who received CERVARIX
164 (0.06%, 20/33,623) and 17 in subjects who received control (0.07%, 17/23,700). Causes of death
165 among subjects were consistent with those reported in adolescent and adult female populations.
166 The most common causes of death were motor vehicle accident (5 subjects who received
167 CERVARIX; 5 subjects who received control) and suicide (2 subjects who received
168 CERVARIX; 5 subjects who received control), followed by neoplasm (3 subjects who received
169 CERVARIX; 2 subjects who received control), autoimmune disease (3 subjects who received
170 CERVARIX; 1 subject who received control), infectious disease (3 subjects who received
171 CERVARIX; 1 subject who received control), homicide (2 subjects who received CERVARIX;
172 1 subject who received control), cardiovascular disorders (2 subjects who received CERVARIX),
173 and death of unknown cause (2 subjects who received control). Among females 10 through 25
174 years of age, 31 deaths were reported (0.05%, 16/29,467 of subjects who received CERVARIX
175 and 0.07%, 15/20,192 of subjects who received control).

176 **6.2 Postmarketing Experience**

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

182 Blood and Lymphatic System Disorders

183 Lymphadenopathy.

184 Immune System Disorders

185 Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema, erythema
186 multiforme.

187 Nervous System Disorders

188 Syncope or vasovagal responses to injection (sometimes accompanied by tonic-clonic
189 movements).

190 **7 DRUG INTERACTIONS**

191 **7.1 Concomitant Vaccine Administration**

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

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

194 **7.2 Hormonal Contraceptives**

195 Among 7,693 subjects 15 through 25 years of age in Study 2 (CERVARIX, N = 3,821 or
196 Hepatitis A Vaccine 720 EL.U., N = 3,872) who used hormonal contraceptives for a mean of
197 2.8 years, the observed efficacy of CERVARIX was similar to that observed among subjects who
198 did not report use of hormonal contraceptives.

199 **7.3 Immunosuppressive Therapies**

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

203 **8 USE IN SPECIFIC POPULATIONS**

204 **8.1 Pregnancy**

205 Pregnancy Category B

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

211 Non-clinical Studies

212 An evaluation of the effect of CERVARIX on embryo-fetal, pre- and post-natal development
213 was conducted using rats. One group of rats was administered CERVARIX 30 days prior to
214 gestation and during the period of organogenesis (gestation Days 6, 8, 11, and 15). A second
215 group of rats was administered saline at 30 days prior to gestation followed by CERVARIX on
216 Days 6, 8, 11, and 15 of gestation. Two additional groups of rats received either saline or
217 adjuvant following the same dosing regimen. CERVARIX was administered at
218 0.1 mL/rat/occasion (approximately 47-fold excess relative to the projected human dose on a
219 mg/kg basis) by intramuscular injection. No adverse effects on mating, fertility, pregnancy,

220 parturition, lactation, or embryo-fetal, pre- and post-natal development were observed. There
221 were no vaccine-related fetal malformations or other evidence of teratogenesis.

222 Clinical Studies

223 *Overall Outcomes:* In pre-licensure clinical studies, pregnancy testing was performed prior to
224 each vaccine administration and vaccination was discontinued if a subject had a positive
225 pregnancy test. In all clinical trials, subjects were instructed to take precautions to avoid
226 pregnancy until 2 months after the last vaccination. During pre-licensure clinical development, a
227 total of 7,276 pregnancies were reported among 3,696 females receiving CERVARIX and 3,580
228 females receiving a control (Hepatitis A Vaccine 360 EL.U., Hepatitis A Vaccine 720 EL.U., or
229 500 mcg Al(OH)₃). The overall proportions of pregnancy outcomes were similar between
230 treatment groups. The majority of women gave birth to normal infants (62.2% and 62.6% of
231 recipients of CERVARIX and control, respectively). Other outcomes included spontaneous
232 abortion (11.0% and 10.8% of recipients of CERVARIX and control, respectively), elective
233 termination (5.8% and 6.1% of recipients of CERVARIX and control, respectively), abnormal
234 infant other than congenital anomaly (2.8% and 3.2% of recipients of CERVARIX and control,
235 respectively), and premature birth (2.0% and 1.7% of recipients of CERVARIX and control,
236 respectively). Other outcomes (congenital anomaly, stillbirth, ectopic pregnancy, and therapeutic
237 abortion) were reported less frequently in 0.1% to 0.8% of pregnancies in both groups.

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

252 A post-hoc analysis was performed on a pooled database of pregnancies with known outcome
253 among women 15 to 25 years of age enrolled in controlled clinical trials (N = 4,670 for
254 CERVARIX and N = 4,689 for pooled control, HAV 360 EL.U., HAV 720 EL.U., or 500 mcg
255 Al(OH)₃). In an analysis of pregnancies with exposure to CERVARIX or control between
256 45 days prior to and 30 days after the LMP, the relative risk of spontaneous abortion was 1.54
257 (95% CI: 0.95, 2.54) for exposure to one dose of CERVARIX (n/N = 46/326) compared with one

258 dose of control (n/N = 33/338) and 1.21 (95% CI: 0.27, 7.33) for exposure to 2 doses of
259 CERVARIX (n/N = 8/71) compared with 2 doses of control (n/N = 3/38).

260 The association between vaccination with CERVARIX and spontaneous abortion was evaluated
261 in a post-marketing, retrospective, observational, cohort study using primary care medical
262 records in the United Kingdom. The study assessed the risk of spontaneous abortion during
263 weeks 1 to 19 of gestation in two cohorts of women 15 to 25 years of age: one cohort who
264 received one or more doses of CERVARIX between 45 days prior to and 30 days after the LMP
265 (close exposure) and another cohort who received the last dose of CERVARIX between
266 18 months and 120 days prior to the LMP (remote exposure). The hazard ratio for spontaneous
267 abortion was 1.26 (95% CI: 0.77, 2.09) for the close-exposure cohort (n/N = 23/207) compared
268 with the remote-exposure cohort (n/N = 56/632). In sensitivity analyses for the close-exposure
269 cohort, the hazard ratio compared with the remote-exposure cohort was 1.07 (95% CI: 0.61,
270 1.86) for women who received only one dose of CERVARIX (n/N = 17/178) and 2.59 (95% CI:
271 1.11, 6.04) for women who received 2 doses of CERVARIX (n/N = 6/29).

272 **8.3 Nursing Mothers**

273 In non-clinical studies in rats, serological data suggest a transfer of anti-HPV-16 and anti-HPV-
274 18 antibodies via milk during lactation in rats. Excretion of vaccine-induced antibodies in human
275 milk has not been studied for CERVARIX. Because many drugs are excreted in human milk,
276 caution should be exercised when CERVARIX is administered to a nursing woman.

277 **8.4 Pediatric Use**

278 Safety and effectiveness in pediatric patients younger than 9 years of age have not been
279 established. The safety and effectiveness of CERVARIX have been evaluated in 1,275 subjects 9
280 through 14 years of age and 6,362 subjects 15 through 17 years of age. [See *Adverse Reactions*
281 (6.1), *Clinical Studies* (14.5).]

282 **8.5 Geriatric Use**

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

286 **8.6 Immunocompromised Individuals**

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

289 **11 DESCRIPTION**

290 CERVARIX [Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant] is a
291 non-infectious recombinant, AS04-adjuvanted vaccine that contains recombinant L1 protein, the
292 major antigenic protein of the capsid, of oncogenic HPV types 16 and 18. The L1 proteins are
293 produced in separate bioreactors using the recombinant Baculovirus expression vector system in

294 a serum-free culture media composed of chemically-defined lipids, vitamins, amino acids, and
295 mineral salts. Following replication of the L1 encoding recombinant Baculovirus in
296 *Trichoplusia ni* insect cells, the L1 protein accumulates in the cytoplasm of the cells. The L1
297 proteins are released by cell disruption and purified by a series of chromatographic and filtration
298 methods. Assembly of the L1 proteins into virus-like particles (VLPs) occurs at the end of the
299 purification process. The purified, non-infectious VLPs are then adsorbed on to aluminum (as
300 hydroxide salt). The adjuvant system, AS04, is composed of 3-*O*-desacyl-4'-monophosphoryl
301 lipid A (MPL) adsorbed on to aluminum (as hydroxide salt).

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

305 CERVARIX is a sterile suspension for intramuscular injection. Each 0.5-mL dose is formulated
306 to contain 20 mcg of HPV type 16 L1 protein, 20 mcg of HPV type 18 L1 protein, 50 mcg of the
307 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL), and 0.5 mg of aluminum hydroxide. Each dose
308 also contains 4.4 mg of sodium chloride and 0.624 mg of sodium dihydrogen phosphate
309 dihydrate. Each dose may also contain residual amounts of insect cell and viral protein (<40 ng)
310 and bacterial cell protein (<150 ng) from the manufacturing process. CERVARIX does not
311 contain a preservative.

312 The tip caps contain natural rubber latex; the plungers are not made with natural rubber latex.

313 **12 CLINICAL PHARMACOLOGY**

314 **12.1 Mechanism of Action**

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

318 **13 NONCLINICAL TOXICOLOGY**

319 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

323 **14 CLINICAL STUDIES**

324 Cervical intraepithelial neoplasia (CIN) Grade 2 and 3 lesions or cervical adenocarcinoma *in situ*
325 (AIS) are the immediate and necessary precursors of squamous cell carcinoma and
326 adenocarcinoma of the cervix, respectively. Their detection and removal has been shown to
327 prevent cancer. Therefore, CIN2/3 and AIS (precancerous lesions) serve as surrogate markers for
328 the prevention of cervical cancer. In clinical studies to evaluate the efficacy of CERVARIX, the

329 endpoints were cases of CIN2/3 and AIS associated with HPV-16, HPV-18, and other oncogenic
330 HPV types. Persistent infection with HPV-16 and HPV-18 that lasts for 12 months was also an
331 endpoint.

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

335 Study 1 (HPV 001) enrolled women who were negative for oncogenic HPV DNA (HPV types
336 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) in cervical samples, seronegative for
337 HPV-16 and HPV-18 antibodies, and had normal cytology. This represents a population
338 presumed “naïve” without current HPV infection at the time of vaccination and without prior
339 exposure to either HPV-16 or HPV-18. Subjects were enrolled in an extended follow-up study
340 (Study 1 Extension [HPV 007]) to evaluate the long-term efficacy, immunogenicity, and safety.
341 These subjects have been followed for up to 6.4 years.

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

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

350 **14.1 Prophylactic Efficacy against HPV Types 16 and 18**

351 Study 2

352 A randomized, double-blind, controlled clinical trial was conducted in which 18,665 healthy
353 females 15 through 25 years of age received CERVARIX or Hepatitis A Vaccine control on a 0-,
354 1-, and 6-month schedule. Among subjects, 54.8% of subjects were white, 31.5% Asian, 7.1%
355 Hispanic, 3.7% black, and 2.9% were of other racial/ethnic groups.

356 In this study, women were randomized and vaccinated regardless of baseline HPV DNA status,
357 serostatus, or cytology. Women with HPV-16 or HPV-18 DNA present in baseline cervical
358 samples (HPV DNA positive) at study entry were considered currently infected with that specific
359 HPV type. If HPV DNA was not detected by PCR, women were considered HPV DNA negative.
360 Additionally, cervical samples were assessed for cytologic abnormalities and serologic testing
361 was performed for anti-HPV-16 and anti-HPV-18 serum antibodies at baseline. Women with
362 anti-HPV serum antibodies present were considered to have prior exposure to HPV and
363 characterized as seropositive. Women seropositive for HPV-16 or HPV-18 but DNA negative for
364 that specific serotype were considered as having cleared a previous natural infection. Women
365 without antibodies to HPV-16 and HPV-18 were characterized as seronegative. Before

366 vaccination, 73.6% of subjects were naïve (without current infection [DNA negative] and
367 without prior exposure [seronegative]) to HPV-16 and/or HPV-18.

368 Efficacy endpoints included histological evaluation of precancerous and dysplastic lesions (CIN
369 Grade 1, Grade 2, or Grade 3), and AIS. Virological endpoints (HPV DNA in cervical samples
370 detected by PCR) included 12-month persistent infection (defined as at least 2 positive
371 specimens for the same HPV type over a minimum interval of 10 months).

372 The according-to-protocol (ATP) cohort for efficacy analyses for HPV-16 and/or HPV-18
373 included all subjects who received 3 doses of vaccine, for whom efficacy endpoint measures
374 were available and who were HPV-16 and/or HPV-18 DNA negative and seronegative at
375 baseline and HPV-16 and/or HPV-18 DNA negative at Month 6 for the HPV type considered in
376 the analysis. Case counting for the ATP cohort started on Day 1 after the third dose of vaccine.
377 This cohort included women who had normal or low-grade cytology (cytological abnormalities
378 including atypical squamous cells of undetermined significance [ASC-US] or low-grade
379 squamous intraepithelial lesions [LSIL]) at baseline and excluded women with high-grade
380 cytology.

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

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

388 The pre-defined final analysis was event-triggered, i.e., performed when at least 36 CIN2/3 or
389 AIS cases associated with HPV-16 or HPV-18 were accrued in the ATP cohort. The mean
390 follow-up after the first dose was approximately 39 months and included approximately 3,300
391 women who completed the Month 48 visit.

392 The pre-defined end-of-study analysis was performed at the end of the 4-year follow-up period
393 (i.e., after all subjects completed the Month 48 visit) and included all subjects from the TVC.
394 The mean follow-up after the first dose was approximately 44 months and included
395 approximately 15,600 women who completed the Month 48 visit.

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

398 **Table 5. Efficacy of CERVARIX against Histopathological Lesions Associated with HPV-**
 399 **16 or HPV-18 in Females 15 through 25 Years of Age (According-to-Protocol Cohort^a)**
 400 **(Study 2)**

	Final Analysis					End-of-Study Analysis				
	CERVARIX		Control ^b		% Efficacy (96.1% CI) ^c	CERVARIX		Control ^b		% Efficacy (95% CI)
	N	n	N	n		N	n	N	n	
CIN2/3 or AIS	7,344	4	7,312	56	92.9 (79.9, 98.3)	7,338	5	7,305	97	94.9 (87.7, 98.4)
CIN1/2/ 3 or AIS	7,344	8	7,312	96	91.7 (82.4, 96.7)	7,338	12	7,305	165	92.8 (87.1, 96.4)

401 CI = Confidence Interval; n = Number of cases.

402 ^a Subjects (including women who had normal cytology, ASC-US, or LSIL at baseline) who
 403 received 3 doses of vaccine and were HPV DNA negative and seronegative at baseline and
 404 HPV DNA negative at Month 6 for the corresponding HPV type (N).

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

406 ^c The 96.1% confidence interval reflected in the final analysis results from statistical adjustment
 407 for the previously conducted interim analysis.

408 Since CIN3 or AIS represents a more immediate precursor to cervical cancer, cases of CIN3 or
 409 AIS associated with HPV-16 or HPV-18 were evaluated. In the ATP cohort, CERVARIX was
 410 efficacious in the prevention of CIN3 or AIS associated with HPV-16 or HPV-18 in the final
 411 analysis (80.0% [96.1% CI: 0.3, 98.1]); these results were confirmed in the end-of-study analysis
 412 (91.7% [95% CI: 66.6, 99.1]).

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

416 Efficacy of CERVARIX against 12-month persistent infection with HPV-16 or HPV-18 was also
 417 evaluated. In the ATP cohort, CERVARIX reduced the incidence of 12-month persistent
 418 infection with HPV-16 and/or HPV-18 by 91.4% (96.1% CI: 86.1, 95.0) in the final analysis;
 419 these results were confirmed in the end-of-study analysis (92.9% [95% CI: 89.4, 95.4]).

420 Immune response following natural infection does not reliably confer protection against future
 421 infections. Among subjects who received 3 doses of CERVARIX and who were seropositive at
 422 baseline and DNA negative for HPV-16 or HPV-18 at baseline and Month 6, CERVARIX
 423 reduced the incidence of 12-month persistent infection by 95.8% (96.1% CI: 72.4, 99.9) in the
 424 final analysis; these results were confirmed in the end-of-study analysis (94.0% [95% CI: 76.7,
 425 99.3]). However, the number of cases of CIN2/3 or AIS was too few in these analyses to
 426 determine efficacy against histopathological endpoints in this population.

427 Study 1 and Study 1 Extension

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

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

440 **14.2 Efficacy against HPV Types 16 and 18, Regardless of Current Infection or**
441 **Prior Exposure to HPV-16 or HPV-18**

442 Study 2

443 The study included women regardless of HPV DNA status (current infection) and serostatus
444 (prior exposure) to vaccine types HPV-16 or HPV-18 at baseline. Efficacy analyses included
445 lesions arising among women regardless of baseline DNA status and serostatus, including HPV
446 infections present at first vaccination and those from infections acquired after Dose 1. In this
447 population, which includes naïve (without current infection and prior exposure) and non-naïve
448 women, CERVARIX was efficacious in the prevention of precancerous lesions or AIS associated
449 with HPV-16 or HPV-18 (Table 6).

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

453 **Table 6. Efficacy of CERVARIX against Disease Associated with HPV-16 or HPV-18 in**
 454 **Females 15 through 25 Years of Age, Regardless of Current or Prior Exposure to Vaccine**
 455 **HPV Types (Study 2)**

	Final Analysis					End-of-Study Analysis				
	CERVARIX		Control ^a		% Efficacy	CERVARIX		Control ^a		% Efficacy
	N	n	N	n	(96.1% CI) ^b	N	n	N	n	(95% CI)
CIN1/2/3 or AIS										
Prophylactic Efficacy ^c	5,449	3	5,436	85	96.5 (89.0, 99.4)	5,466	5	5,452	141	96.5 (91.6, 98.9)
HPV-16 or 18 DNA Positive at Baseline ^d	641	90	592	92	—	642	99	593	101	—
Regardless of Baseline Status ^e	8,667	107	8,682	240	55.5 ^f (43.2, 65.3)	8,694	121	8,708	324	62.9 ^f (54.1, 70.1)
CIN2/3 or AIS										
Prophylactic Efficacy ^c	5,449	1	5,436	63	98.4 (90.4, 100)	5,466	1	5,452	97	99.0 (94.2, 100)
HPV-16 or 18 DNA Positive at Baseline ^d	641	74	592	73	—	642	80	593	82	—
Regardless of Baseline Status ^e	8,667	82	8,682	174	52.8 ^f (37.5, 64.7)	8,694	90	8,708	228	60.7 ^f (49.6, 69.5)
CIN3 or AIS										
Prophylactic Efficacy ^c	5,449	0	5,436	13	100 (64.7, 100)	5,466	0	5,452	27	100 (85.5, 100)
HPV-16 or 18 DNA Positive at Baseline ^d	641	41	592	38	—	642	48	593	47	—
Regardless of Baseline Status ^e	8,667	43	8,682	65	33.6 ^f (-1.1, 56.9)	8,694	51	8,708	94	45.7 ^f (22.9, 62.2)

456 CI = Confidence Interval; n = Number of histopathological cases associated with HPV-16 and/or
 457 HPV-18.

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

459 ^a Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg Al(OH)₃].

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

- 462 ^c TVC naïve: Includes all vaccinated subjects (who received at least one dose of vaccine) who
463 had normal cytology, were HPV DNA negative for 14 oncogenic HPV types, and
464 seronegative for HPV-16 and HPV-18 at baseline (N). Case counting started on Day 1 after
465 the first dose.
- 466 ^d TVC subset: Includes all vaccinated subjects (who received at least one dose of vaccine) who
467 were HPV DNA positive for HPV-16 or HPV-18 irrespective of serostatus at baseline (N).
468 Case counting started on Day 1 after the first dose.
- 469 ^e TVC: Includes all vaccinated subjects (who received at least one dose of vaccine) irrespective
470 of HPV DNA status and serostatus at baseline (N). Case counting started on Day 1 after the
471 first dose.
- 472 ^f Observed vaccine efficacy includes the prophylactic efficacy of CERVARIX and the impact
473 of CERVARIX on the course of infections present at first vaccination.

474 **14.3 Efficacy against Cervical Disease Irrespective of HPV Type, Regardless of**
475 **Current or Prior Infection with Vaccine or Non-vaccine HPV Types**

476 Study 2

477 The impact of CERVARIX against the overall burden of HPV-related cervical disease results
478 from a combination of prophylactic efficacy against, and disease contribution of, HPV-16, HPV-
479 18, and non-vaccine HPV types.

480 In the population naïve to oncogenic HPV (TVC naïve), CERVARIX reduced the overall
481 incidence of CIN1/2/3 or AIS, CIN2/3 or AIS, and CIN3 or AIS regardless of the HPV DNA
482 type in the lesion (Table 7). In the population of women naïve and non-naïve (TVC), vaccine
483 efficacy against CIN1/2/3 or AIS, CIN2/3 or AIS, and CIN3 or AIS was demonstrated in all
484 women regardless of HPV DNA type in the lesion (Table 7).

485 **Table 7. Efficacy of CERVARIX in Prevention of CIN or AIS Irrespective of Any HPV**
 486 **Type in Females 15 through 25 Years of Age, Regardless of Current or Prior Infection with**
 487 **Vaccine or Non-vaccine Types (Study 2)**

	Final Analysis					End-of-Study Analysis				
	CERVARIX		Control ^a		% Efficacy (96.1% CI) ^b	CERVARIX		Control ^a		% Efficacy (95% CI)
	N	n	N	n		N	n	N	n	
CIN1/2/3 or AIS										
Prophylactic Efficacy ^c	5,449	106	5,436	211	50.1 (35.9, 61.4)	5,466	174	5,452	346	50.3 (40.2, 58.8)
Irrespective of HPV DNA at Baseline ^d	8,667	451	8,682	577	21.7 (10.7, 31.4)	8,694	579	8,708	798	27.7 (19.5, 35.2)
CIN2/3 or AIS										
Prophylactic Efficacy ^c	5,449	33	5,436	110	70.2 (54.7, 80.9)	5,466	61	5,452	172	64.9 (52.7, 74.2)
Irrespective of HPV DNA at Baseline ^d	8,667	224	8,682	322	30.4 (16.4, 42.1)	8,694	287	8,708	428	33.1 (22.2, 42.6)
CIN3 or AIS										
Prophylactic Efficacy ^c	5,449	3	5,436	23	87.0 (54.9, 97.7)	5,466	3	5,452	44	93.2 (78.9, 98.7)
Irrespective of HPV DNA at Baseline ^d	8,667	77	8,682	116	33.4 (9.1, 51.5)	8,694	86	8,708	158	45.6 (28.8, 58.7)

488 CI = Confidence Interval; n = Number of cases.

489 ^a Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg Al(OH)₃].

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

492 ^c TVC naïve: Includes all vaccinated subjects (who received at least one dose of vaccine) who
 493 had normal cytology, were HPV DNA negative for 14 oncogenic HPV types (including
 494 HPV-16 and HPV-18), and seronegative for HPV-16 and HPV-18 at baseline (N). Case
 495 counting started on Day 1 after the first dose.

496 ^d TVC: Includes all vaccinated subjects (who received at least one dose of vaccine) irrespective
 497 of HPV DNA status and serostatus at baseline (N). Case counting started on Day 1 after the
 498 first dose.

499 In exploratory end-of-study analyses, CERVARIX reduced definitive cervical therapy
 500 procedures (includes loop electrosurgical excision procedure [LEEP], cold-knife Cone, and laser
 501 procedures) by 33.2% (95% CI: 20.8, 43.7) in the TVC and by 70.2% (95% CI: 57.8, 79.3) in the
 502 TVC naïve.

503 To assess reductions in disease caused by non-vaccine HPV types, analyses were conducted
 504 combining 12 non-vaccine oncogenic HPV types, including and excluding lesions in which

505 HPV-16 or HPV-18 were also detected. Among females who received 3 doses of CERVARIX
506 and were DNA negative for the specific HPV type at baseline and Month 6, CERVARIX
507 reduced the incidence of CIN2/3 or AIS in the final analysis by 54.0% (96.1% CI: 34.0, 68.4)
508 and 37.4% (96.1% CI: 7.4, 58.2), respectively. In the end-of-study analysis, CERVARIX
509 reduced the incidence of CIN2/3 or AIS by 46.8% (95% CI: 30.7, 59.4) and 24.1% (95% CI: -
510 1.5, 43.5), respectively.

511 End-of-study analyses were conducted to assess the impact of CERVARIX on CIN2/3 or AIS
512 due to specific non-vaccine HPV types. The ATP cohort for these analyses included all subjects
513 irrespective of serostatus who received 3 doses of CERVARIX and were DNA negative for the
514 specific HPV type at baseline and Month 6. These analyses were also conducted in the TVC-
515 naïve population.

516 In analyses including lesions in which HPV-16 or HPV-18 were also detected, vaccine efficacy
517 in prevention of CIN2/3 or AIS associated with HPV-31 was 87.5% (95% CI: 68.3, 96.1) and
518 89.4% (95% CI: 65.5, 97.9), respectively. In analyses excluding lesions in which HPV-16 or
519 HPV-18 were detected, vaccine efficacy in prevention of CIN2/3 or AIS associated with HPV-31
520 was 84.3% (95% CI: 59.5, 95.2) and 83.4% (95% CI: 43.3, 96.9), respectively.

521 **14.4 Immunogenicity**

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

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

528 Duration of Immune Response

529 The duration of immunity following a complete schedule of immunization with CERVARIX has
530 not been established. In Study 1 and Study 1 Extension, the immune response against HPV-16
531 and HPV-18 was evaluated for up to 76 months post-Dose 1, in females 15 through 25 years of
532 age. Vaccine-induced geometric mean titers (GMTs) for both HPV-16 and HPV-18 peaked at
533 Month 7 and thereafter reached a plateau that was sustained from Month 18 up to Month 76. At
534 all timepoints, >98% of subjects were seropositive for both HPV-16 (≥ 8 EL.U./mL, the limit of
535 detection) and HPV-18 (≥ 7 EL.U./mL, the limit of detection) by ELISA.

536 In Study 2, immunogenicity was measured by seropositivity rates and GMTs for ELISA and
537 PBNA (Table 8). The ATP cohort for immunogenicity included all evaluable subjects for whom
538 data concerning immunogenicity endpoint measures were available. These included subjects for
539 whom assay results were available for antibodies against at least one vaccine type. Subjects who
540 acquired either HPV-16 or HPV-18 infection during the trial were excluded.

541 **Table 8. Persistence of Anti-HPV Geometric Mean Titers (GMTs) and Seropositivity Rates**
 542 **for HPV-16 and HPV-18 for Initially Seronegative Females 15 through 25 Years of Age**
 543 **(According-to-Protocol Cohort for Immunogenicity^a) (Study 2)**

Time Point	N	% Seropositive (95% CI)	GMT (95% CI)
Anti-HPV-16 ELISA^b (EL.U./mL)			
Month 7	816	99.5	9,120.0 (8,504.9, 9,779.7)
Month 12	793	99.7	3,266.3 (3,043.3, 3,505.6)
Month 24	755	99.9	1,587.7 (1,484.8, 1,697.7)
Month 36	759	100	1,281.7 (1,198.3, 1,370.9)
Month 48	746	100	1,174.3 (1,096.1, 1,258.0)
Anti-HPV-18 ELISA^b (EL.U./mL)			
Month 7	879	99.4	4,682.9 (4,388.8, 4,996.7)
Month 12	853	100	1,514.7 (1,422.3, 1,613.0)
Month 24	810	99.9	702.2 (655.2, 752.6)
Month 36	817	100	538.1 (502.0, 576.8)
Month 48	806	99.8	476.2 (443.2, 511.6)
Anti-HPV-16 PBNA^c (ED₅₀)			
Month 7	46	100	26,457.0 (19,167.5, 36,518.6)
Month 12	45	100	7,885.5 (5,500.4, 11,304.8)
Month 24	46	100	3,396.4 (2,388.0, 4,830.6)
Month 36	41	100	2,245.1 (1,616.6, 3,117.9)
Month 48	41	97.6	1,931.1 (1,294.4, 2,880.8)
Anti-HPV-18 PBNA^c (ED₅₀)			
Month 7	46	100	8,413.9 (6,394.7, 11,070.7)
Month 12	45	97.8	1,748.2 (1,223.6, 2,497.7)
Month 24	46	100	1,552.5 (1,112.9, 2,165.5)
Month 36	41	100	1,326.9 (948.0, 1,857.3)
Month 48	41	95.1	1,078.1 (714.9, 1,625.6)

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

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

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

551 **14.5 Bridging of Efficacy from Women to Adolescent Girls**

552 The immunogenicity of CERVARIX was evaluated in 3 clinical studies involving 1,275 girls 9
 553 through 14 years of age who received at least one dose of CERVARIX.

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

561 **Table 9. Geometric Mean Titers (GMTs) at Months 7 and 18 for Initially Seronegative**
 562 **Females 10 through 14 Years of Age (According-to-Protocol Cohort for Immunogenicity^a)**
 563 **(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)

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

566 In Study 4 (HPV 012), the immunogenicity of CERVARIX administered to girls 10 through
 567 14 years of age was compared with that in females 15 through 25 years of age. The immune
 568 response in girls 10 through 14 years of age measured one month post-Dose 3 was non-inferior
 569 to that seen in females 15 through 25 years of age for both HPV-16 and HPV-18 antigens
 570 (Table 10).

571 **Table 10. Geometric Mean Titers (GMTs) and Seropositivity Rates at Month 7 for Initially**
 572 **Seronegative Females 10 through 14 Years of Age Compared with Females 15 through 25**
 573 **Years of 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

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

576 ^b Non-inferiority based on the upper limit of the 2-sided 95% CI for the GMT ratio (15- through
 577 25-year olds/10- through 14-year olds) was < 2 .

578 ^c Non-inferiority based on the upper limit of the 2-sided 95% CI for the difference between the
 579 seropositivity rates for 10- through 14-year olds and 15- through 25-year olds was $< 10\%$.

580 In Study 5, a post-hoc analysis compared the immunogenicity of CERVARIX administered to
581 girls 9 through 14 years of age (n = 68) with that in females 15 through 25 years of age
582 (n = 114). In these initially seronegative subjects, the immune response in girls 9 through
583 14 years of age measured one month post-Dose 3 was non-inferior to that observed in females 15
584 through 25 years of age for both HPV-16 and HPV-18 antigens [lower limit of the 2-sided 95%
585 CI for the GMT ratio (9- through 14-year olds/15- through 25-year olds) was >0.5]. The GMTs
586 for anti-HPV-16 and anti-HPV-18 antibodies at Month 7 were 22,261.3 EL.U./mL and
587 7,398.8 EL.U./mL, respectively, in girls 9 through 14 years of age and 10,322.0 EL.U./mL and
588 4,261.5 EL.U./mL, respectively, in females 15 through 25 years of age.

589 Based on these immunogenicity data, the efficacy of CERVARIX is inferred in girls 9 through
590 14 years of age.

591 **16 HOW SUPPLIED/STORAGE AND HANDLING**

592 CERVARIX is available in 0.5-mL single-dose disposable prefilled TIP-LOK syringes
593 (packaged without needles):

594 NDC 58160-830-05 Syringe in Package of 1: NDC 58160-830-34

595 NDC 58160-830-43 Syringe in Package of 10: NDC 58160-830-52

596 Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has
597 been frozen. Upon storage, a fine, white deposit with a clear, colorless supernatant may be
598 observed. This does not constitute a sign of deterioration.

599 **17 PATIENT COUNSELING INFORMATION**

600 Advise the patient to read the FDA-approved patient labeling (Patient Information). Patient
601 labeling is provided as a tear-off leaflet at the end of this Full Prescribing Information.

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

605 Inform the patient, parent, or guardian:

- 606 • Vaccination does not substitute for routine cervical cancer screening. Women who receive
607 CERVARIX should continue to undergo cervical cancer screening per standard of care.
- 608 • CERVARIX does not protect against disease from HPV types to which a woman has
609 previously been exposed through sexual activity.
- 610 • Since syncope has been reported following vaccination in young females, sometimes
611 resulting in falling with injury, observation for 15 minutes after administration is
612 recommended.
- 613 • Safety has not been established in pregnant women.

614 CERVARIX and TIP-LOK are registered trademarks of the GSK group of companies.



615

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623

PATIENT INFORMATION

624

CERVARIX[®] (SERV-ah-rix)

625

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

626

627 Read this Patient Information carefully before getting CERVARIX. You (the person
628 getting CERVARIX) will need 3 doses of the vaccine. Read this information before
629 each dose of CERVARIX. This information does not take the place of talking with
your healthcare provider about CERVARIX.

630

What is CERVARIX?

631

632 CERVARIX is a vaccine given by injection (shot) to girls and women 9 through 25
years of age.

633

- CERVARIX helps protect against cervical cancer and precancers caused by
634 human papillomavirus (HPV) types 16 and 18.

635

- There are many types of HPV but only certain types cause cervical cancer. HPV
636 types 16 and 18 are the 2 most common types of HPV that lead to cervical
637 cancer and precancers.

638

- Abnormal Pap smear results can indicate the presence of precancers. Some
639 precancers can lead to cervical cancer.

640

- CERVARIX is not a treatment for HPV.

641

- You can not get HPV diseases from CERVARIX.

642

What important information should I know about CERVARIX?

643

- You should continue to get routine cervical cancer screening (such as a Pap
644 smear).

645

- CERVARIX may not fully protect everyone who gets the vaccine.

646

- Not all cervical cancers are caused by the HPV types CERVARIX protects against.
647 CERVARIX will not protect against diseases from all HPV types.

648

- CERVARIX will not protect against HPV types that you already have.

649

Who should not get CERVARIX?

650

You should not get CERVARIX if you have or have had:

651

- an allergic reaction to a previous dose of CERVARIX.

652

- an allergy to any of the ingredients in CERVARIX (listed below).

653

What should I tell my healthcare provider before getting CERVARIX?

654

Tell your healthcare provider about all your health conditions, including if you:

655

- have had an allergic reaction after a previous dose of CERVARIX.

656

- have an allergy to latex.

657

- have a weakened immune system.

- 658 • are taking any other medicine or have recently gotten any other vaccine.
659 • have a fever over 100°F (37.8°C).
660 • are pregnant or are planning to get pregnant during the time period of the 3
661 shots. CERVARIX is not recommended for use in pregnant women.

662 Your healthcare provider will decide if you should get CERVARIX.

663 **How is CERVARIX given?**

664 CERVARIX is given as an injection (shot) in a muscle in your arm.

665 You will need a total of 3 shots as follows:

- 666 • First dose: given at a time decided by you and your healthcare provider
667 • Second dose: given 1 month after the first dose
668 • Third dose: given 6 months after the first dose

669 Fainting may occur, sometimes resulting in falling with injury, especially in young
670 females. Your healthcare provider may ask you to sit or lie down for 15 minutes
671 after you get CERVARIX. Some people who faint may shake or become stiff. If this
672 happens, it may require evaluation or treatment by your healthcare provider.

673 Make sure you get all 3 doses on time for the best protection. If you miss a
674 scheduled dose, talk to your healthcare provider.

675 **What are the possible side effects of CERVARIX?**

676 The most common side effects of CERVARIX are:

- 677 • pain, redness, and swelling where you got the shot
678 • feeling tired
679 • headache
680 • muscle aches
681 • nausea, vomiting, diarrhea, and stomach pain
682 • joint aches

683 Other possible side effects include:

- 684 • swollen glands (neck, armpit, or groin).

685 Call your healthcare provider or seek medical treatment immediately if you develop
686 hives, difficulty breathing, or swelling of the throat, because these may be signs of
687 a severe allergic reaction.

688 Tell your healthcare provider about these or any other side effects that concern
689 you. For a more complete list of side effects, ask your healthcare provider.

690 **What are the ingredients in CERVARIX?**

691 CERVARIX contains proteins of HPV types 16 and 18. The vaccine also contains 3-
692 *O*-desacyl-4'-monophosphoryl lipid A (MPL), aluminum hydroxide, sodium chloride,
693 and sodium dihydrogen phosphate dehydrate.

694 CERVARIX contains no preservatives.

695 This is a summary of information about CERVARIX. If you would like more
696 information, please talk with your healthcare provider or visit www.cervarix.com.

697 CERVARIX is a registered trademark of the GSK group of companies.



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704 Month YEAR

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