Drug and Biologic Coverage Policy

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Coverage Policy Number 6018

Human Papillomavirus Vaccine

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Related Coverage Resources

Preventive Care Services
Routine Immunizations

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

The Affordable Care Act (ACA) requires individual and group health plans to cover in-network routine immunizations without cost sharing (e.g., deductibles, coinsurance, copayments) unless the plan qualifies under the grandfather provision or for an exemption. Coverage of routine immunizations is generally subject to the terms, conditions and limitations of a preventive services benefit as described in the applicable plan's schedule of copayments. Please refer to the applicable benefit plan document to determine benefit availability and the terms and conditions of coverage. Many benefit plans specifically exclude immunizations that are for the purpose of travel or to protect against occupational hazards and risks.

If coverage is available under the Benefit plan, the following conditions of coverage apply:

Human papillomavirus (HPV) vaccine is covered as medically necessary as recommended by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP):

- **Bivalent human papillomavirus recombinant vaccine (Cervarix) for females age 9 years through 25 years of age†**
- **Quadrivalent human papillomavirus recombinant vaccine (Gardasil) for females and males age 9 years through 26 years of age†**

- **9-Valent human papillomavirus recombinant vaccine (Gardasil 9) for females and males age 9 years through 26 years of age and for ages 27 through 45 years based on shared clinical decision making†**

†**Note: Age criteria apply to Dates of Service prior to 02/16/2019**

FDA Approved Indications

FDA Approved Indications

Cervarix

Cervarix is 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

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

Gardasil

Gardasil is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine:

- Cervical, vulvar, vaginal and anal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

Males

Gardasil is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine:

- Anal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

Gardasil 9

Gardasil 9 is a vaccine indicated in girls and women 9 through 45 years of age for the prevention of the following diseases:

- Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58.
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma *in situ* (AIS).
- Cervical intraepithelial neoplasia (CIN) grade 1.
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3.
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3.
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

Males

Gardasil 9 is indicated in boys and men 9 through 45 years of age for the prevention of the following diseases

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

Recommended Dosing

FDA Recommended Dosing

Cervarix
Cervarix should be administered intramuscularly as a 0.5-mL dose at the following schedule: 0, 1, and 6 months.

Gardasil
Gardasil should be administered intramuscularly as a 0.5-mL dose at the following schedule: 0, 2 months, and 6 months.

Gardasil 9
Gardasil 9 should be administered intramuscularly as a 0.5-mL dose at the following schedule:
Age 9 through 14 years: 2-dose regimen at 0, 6 to 12 months*
Age 9 through 14 years: 3-dose regimen at 0, 2, 6 months
(*If the second dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the second dose.
Age 15 through 45 years: 3 dose regimen at 0, 2, 6 months

Vaccine Availability

In May 2017 Gardasil 9 (9-valent HPV vaccine) became the only HPV vaccine available in the United States.

General Background

Disease Overview
Genital HPV infections are the most common sexually-transmitted diseases in the United States. There are more than 40 types of HPV. In most cases, HPV goes away on its own without causing any health problems however, certain high-risk types of HPV that persist can cause cervical cancer and other, less common cancers, including cancers of the anus, penis, vulva, and vagina. Some HPV types can cause genital warts.

Pharmacology
Cervarix and Gardasil are non-infectious recombinant vaccines. Cervarix is prepared from the protein of HPV types 16 and 18. Gardasil is prepared from the protein of HPV Types 6, 11, 16, and 18. Gardasil 9 is prepared from the protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. HPV types 16 and 18 are the two types of HPV believed responsible for about 70% of cervical cancer cases, and types 6 and 11 cause 90% of genital wart cases. All virus types are sexually transmitted.

Professional Societies/Organizations
The Advisory Committee on Immunization Practices
ACIP recommends routine HPV vaccination at age 11 or 12 years. Vaccination can be given starting at age 9 years. ACIP also recommends vaccination for males and females through age 26 years. Vaccination for individuals 27 through 45 years of age who are not adequately vaccinated is recommended based on shared clinical decision making.

- For persons initiating vaccination before their 15th birthday, the recommended immunization schedule is 2 doses of HPV vaccine. The second dose should be administered 6–12 months after the first dose (0, 6–12 month schedule).
- For persons initiating vaccination on or after their 15th birthday, the recommended immunization schedule is 3 doses of HPV vaccine. The second dose should be administered 1–2 months after the first dose, and the third dose should be administered 6 months after the first dose (0, 1–2, 6 month schedule).
- Persons who initiated vaccination with Gardasil 9, Gardasil, or Cervarix before their 15th birthday, and received 2 doses of any HPV vaccine at the recommended dosing schedule (0, 6–12 months), or 3 doses of any HPV vaccine at the recommended dosing schedule (0, 1–2, 6 months), are considered adequately vaccinated.

- Persons who initiated vaccination with Gardasil 9, Gardasil, or Cervarix on or after their 15th birthday, and received 3 doses of any HPV vaccine at the recommended dosing schedule, are considered adequately vaccinated.
- Gardasil 9 may be used to continue or complete a vaccination series started with Gardasil or Cervarix.
- For persons who have been adequately vaccinated with Cervarix or Gardasil, there is no ACIP recommendation regarding additional vaccination with Gardasil 9. [Morbidity and Mortality Report (MMWR) December 2016]

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative:
No recommendations are available for Human Papillomavirus Vaccine.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)
There are no CMS National Coverage Determinations for Human Papillomavirus Vaccine.

Clinical Efficacy
Cervarix
The primary clinical study for Cervarix included more than 18,000 women ages 15 years through 25 years in the United States and 11 other countries. Of these women, about 9,000 received Cervarix and 9,000 received Havrix, a licensed hepatitis A virus vaccine, as a control. The results showed that among women who had not already been infected by HPV types 16 and/or 18 before the start of the study, Cervarix was about 93 percent effective in preventing precancerous cervical lesions caused by these HPV types. Among all Cervarix vaccinees, which included those who tested negative for HPV 16 and/or 18, and those who tested positive at the start of the study, Cervarix was approximately 53 percent effective in preventing precancerous cervical lesions.

Studies also were performed to measure the immune response to Cervarix in girls ages 10 years through 14 years. Their immune response was similar to that of women ages 15 years through 25 years, indicating that the vaccine should have similar effectiveness in the 10 through 14 year age group.

Clinical data from one randomized, single-blind multicenter study of 961 females was the basis for FDA licensure for use in females 9 through 25 years of age.

Gardasil
Four double-blind, placebo-controlled, randomized Phase II and Phase III clinical studies evaluated the efficacy and safety of Gardasil in 20,541 women aged 16-26 years. Patients were followed for up to five years after enrollment. In the combined analyses, Gardasil prevented the following:
- 100% of HPV 16- and 18- related cervical precancers and noninvasive cervical cancers
- 95% of low-grade cervical lesions and cervical precancers caused by HPV 6, 11, 16 or 18
- 99% of cases of genital warts caused by HPV 6 or 11
- 100% of HPV 16- and 18-related vulvar and vaginal precancers in women not previously exposed to the relevant HPV types

A randomized, double-blind, placebo-controlled trial study was designed to examine the efficacy of Gardasil in 4,055 men aged 16 to 26 years against HPV 6/11/16/18-related external genital lesions and infection. External genital lesions include: external genital warts, penile/perineal/perianal intraepithelial neoplasia (PIN), and penile/perineal/perianal cancer. Study participants included men who were naïve to the relevant HPV type at the start of the study and through month seven (one month after completion of the three-dose series). All three doses did not deviate from the study, and endpoints were counted starting after month seven (Per Protocol Efficacy Population [PPE]). The results included:
- 90.4 percent efficacy (95 percent CI: 69.2, 98.1) against any HPV 6/11/16/18-related external genital lesion
- 89.4 percent efficacy (95 percent CI: 65.5, 97.9) against condyloma and 100 percent against PIN (95 percent CI: <0, 100)
- 85.6 percent efficacy (97.5 percent CI: 73.4, 92.9) against HPV 6/11/16/18 (persistent infection is when the same HPV type is detected through swabs or biopsies over two or more consecutive visits six months apart)
- 44.7 percent efficacy (95 percent CI: 31.5, 55.6) against DNA detection at one or more visits

Gardasil 9
A randomized, double-blind, comparator-controlled clinical trial to evaluate the efficacy, immunogenicity, and safety of Gardasil 9 was conducted that included 14,204 females ages 16 through 26 years. Participants received either Gardasil or Gardasil 9. Gardasil 9 was determined to be 96.7 percent effective (95% CI: 80.9, 99.8) in preventing cervical, vulvar and vaginal cancers caused by the five additional HPV types (31, 33, 45, 52, and 58). Gardasil 9 was found to be as effective as Gardasil for the prevention of diseases caused by the four shared HPV types (6, 11, 16, and 18) based on similar antibody responses in participants.

A randomized, multi-centered clinical trial evaluated the immunogenicity and safety of Gardasil 9 in 2534 children ages 9 through 15 years (1890 females/644 males) and 465 young women ages 16 through 26 years. The results showed that antibody Geometic Mean Titers (GMT) and seroconversion rates for month 7 for each of the Gardasil 9 HPV vaccine types were non-inferior for females and males in the 9-15 year age group compared with the 16-26 year female group. Results support the bridging of efficacy findings in 16- to 26-year-old women to 9- to 15-year-old children.

A randomized, double-blind, controlled multicenter clinical trial studied the immunogenicity of Gardasil 9 compared with Gardasil in 600 females age 9 through 15 years. All participants were randomized to a standard 3-dose regimen of either Gardasil or Gardasil 9. Non-inferiority of anti-HPV antibodies following Gardasil 9 compared to Gardasil were demonstrated and the overall safety profile was similar to Gardasil.

Clinical data from an open-label, multicenter clinical trial on the safety and immunogenicity of Gardasil 9 in 1400 males compared to 1100 females was the basis for FDA licensure in males age 16 through 26 years of age. The effectiveness of Gardasil 9 in males was inferred by immunobridging strategy with females.

An open-label, multicenter clinical trial of 1518 females and males was the basis for FDA licensure for the 2-dose regimen of Gardasil 9 administered at 1 and 6 months (or 0 and 12 months) to girls and boys 9 to 14 years of age.

On October 5, 2018, Gardasil 9 received FDA licensure for females and males age 27 through 45 years of age based on an initial base study and a longer-term follow-up study. The base study was a 4-year randomized, double-blind, placebo controlled, multi-center study of 3815 women age 27 through age 45 years. The efficacy of Gardasil against the combined incidence of HPV 6-, 11-, 16-, 18-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, cervical dysplasia (any grade CIN), AIS and cervical cancer in the PPE population was 87% (95% CI: 75.4%, 94.6%). In the same population, the efficacy of Gardasil against the combined incidence of HPV 6-, 11-, 16, 18-related genital warts or cervical dysplasia was 95.0% (95% CI: 68.7%, 99.9%). In the long term extension study, no cases of HPV 6-, 11-, 16-, 18-related CIN (any grade) or genital wars were observed in the PPE population. The data supported the duration of protection against genital warts and CIN (any grade) due to vaccine-type (6/11/16/18) HPV disease in women 27 through 45 years of age. Effectiveness in women 27 through 45 years of age for the additional 5 HPV types in Gardasil 9 is extrapolated based on clinical efficacy data from women 16 through 26 years of age. The effectiveness of Gardasil 9 in men 27 through 45 years of age is inferred from efficacy data in women 27 through 45 years of age and by immunogenicity data from a clinical trial in which 150 men, 27 through 45 years of age, received a 3-dose regimen of Gardasil. Effectiveness in males in this age group for the additional 5 HPV types in Gardasil 9 is extrapolated similar to those described for women.

Limitations, Warnings and Precautions
Cervarix/Gardasil/Gardasil 9
Cervarix and Gardasil/Gardasil 9 do not provide protection against disease due to all HPV types and have not been demonstrated to provide protection against disease from any HPV type to which an individual has previously been exposed through sexual activity. Vaccination does not substitute for routine cervical cancer screening. Women who receive Cervarix and Gardasil/Gardasil 9 should continue to undergo cervical cancer screening per standard of care. Safety and effectiveness of Cervarix and Gardasil/Gardasil 9 have not been established in children younger than 9 years of age. HPV vaccines are not recommended for use in pregnant women. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose series should be delayed until completion of pregnancy. Pregnancy testing is not needed before vaccination. If a vaccine dose has been administered during pregnancy, no intervention is needed. Exposure to Cervarix and

Gardasil/Gardasil 9 during pregnancy should be reported to Vaccine Adverse Event Reporting System (VAERS) and to the established vaccine in pregnancy registry. Immunocompromised individuals may have a reduced immune response. Brief fainting spells and related symptoms (such as jerking movements) may develop after vaccination with Cervarix and Gardasil/Gardasil 9. Sitting or lying down for about 15 minutes after vaccination, as is recommended for all vaccines, can help prevent fainting and injuries caused by falls. Injection site pain, redness and swelling are common adverse reactions.

Gardasil/Gardasil 9
Gardasil/Gardasil 9 are not intended to be used for treatment of active external genital lesions; cervical, vulvar, vaginal and anal cancers; CIN, VIN, VaIN, or AIN. Gardasil/Gardasil 9 have not been demonstrated to protect against diseases due to HPV types not contained in the vaccine. Not all vulvar and vaginal cancers are caused by HPV, and the vaccine protects only against those vulvar, vaginal, and anal cancers caused by HPV 16 and 18 (Gardasil/Gardasil 9) and HPV 31, 33, 45, 52, 58 (Gardasil 9). Gardasil/Gardasil 9 does not protect against genital diseases not caused by HPV. Vaccination with Gardasil/Gardasil 9 may not result in protection in all vaccine recipients. Recipients of Gardasil/Gardasil 9 should not discontinue anal cancer screening if it has been recommended by a health care provider. The effectiveness of Gardasil/Gardasil 9 has not been established in children below the age of 9 years.

Coding/ Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
90649†	Human Papillomavirus vaccine, types 6, 11, 16, 18 quadrivalent (4vHPV), 3 dose schedule, for intramuscular use
90650†	Human Papillomavirus vaccine, types 16, 18, bivalent (2vHPV), 3 dose schedule, for intramuscular use
90651†	Human Papillomavirus vaccine types 6, 11, 16, 18, 31, 33, 45, 52, 58, nonavalent (9vHPV), 2 or 3 dose schedule, for intramuscular use

†**Note: Age criteria apply to Dates of Service prior to 02/16/2019**

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