



CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject **Quadrivalent Human
Papillomavirus (Types 6, 11, 16,
18) Recombinant Vaccine –
(Gardasil®)**

Effective Date.....10/15/2010
Next Revision Date.....10/15/2011
Coverage Position Number..... 6018

Table of Contents

Coverage Policy	1
General Background	2
Coding/Billing Information	4
References	4

Hyperlink to Related Coverage Positions

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), 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 participant'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 participant's benefit plan document **always supercedes** 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 group 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. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

Note: Vaccines are covered under most CIGNA medical plans which include a Preventive Benefit. Please refer to the applicable benefit plan document to determine benefit availability and the terms and conditions of coverage.

If coverage is available for vaccines, then:

CIGNA covers quadrivalent human papillomavirus (HPV) recombinant vaccine (Gardasil®) as medically necessary for EITHER of the following:

- prevention of infection from HPV serotypes 6, 11, 16, and 18 in females age 9 to 26
- prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11 in males age 9 to 26 at the discretion of the treating physician

or as currently recommended by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP)

FDA Approved Indications

Females

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, and vaginal 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

Males

Gardasil is indicated in boys and men 9 through 26 years of age for the prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11.

FDA Recommended Dosing

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

Drug Availability

All presentations for Gardasil contain a suspension of 120 mcg L1 protein from HPV types 6, 11, 16, and 18 in a 0.5-mL dose. Gardasil is supplied in vials and syringes in a carton of one 0.5-mL single-dose vial or a carton of ten 0.5-mL single-dose vials. A carton of six 0.5-mL single-dose prefilled Luer Lock syringes, preassembled with UltraSafe Passive₂ delivery system and a carton of six 0.5-mL single-dose prefilled Luer Lock syringes with tip caps are also available.

General Background

Pharmacology

Gardasil is a noninfectious recombinant, quadrivalent vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. This vaccine is designed to protect against HPV types 6, 11, 16, 18. Types 16 and 18 are the two types of human papillomavirus (HPV) believed responsible for about 70% of cervical cancer cases, and types 6 and 11 cause 90% of genital wart cases. All four virus types are sexually transmitted. HPV infects only humans, but animal studies with analogous papillomaviruses suggest that the efficacy of L1 VLP vaccines is mediated by the development of humoral immune responses. Gardasil has been developed based on technology developed at the National Institutes of Health (NIH), and it is comprised of noninfectious VLPs of each HPV type in various amounts and formulations. Gardasil is indicated to prevent cervical cancer and cervical, vulvar, and vaginal precancers, genital warts and low-grade cervical lesions in girls and women 9–26 years of age

Disease Overview

All types of HPV can cause mild pap test abnormalities which do not have serious consequences. Approximately 10 of the 30 identified genital HPV types can lead, in rare cases, to the development of cervical cancer. Research has shown that for about 90% of women, cervical HPV infection becomes undetectable within two years. Although only a small proportion of women have persistent infection, persistent infection with "high-risk" types of HPV is the main risk factor for cervical cancer.

Guidelines

On June 29, 2006, the Advisory Committee on Immunization Practices (ACIP) recommended that Gardasil be routinely given to girls 11–12 years old. The ACIP recommendation also allows for vaccination of girls beginning at 9 and 10 years old at the discretion of the physician and health care provider. The committee also recommends a "catch-up" vaccination in girls and women 13–26 years old, since they will benefit from getting the vaccine.

In October 2009, the FDA approved use of Gardasil in boys and men ages 9-26 for the prevention of genital warts; however, the ACIP provided a provisional recommendation in which the committee voted to advise

physicians that they are free to recommend Gardasil in boys and men but stopped short of making a routine-vaccination recommendation.

Clinical Efficacy

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

In these studies, Gardasil was generally well tolerated and only 0.1% discontinued use due to adverse events.

A randomized, double-blind, placebo-controlled trial study was designed to examine the efficacy of Gardasil in 4,065 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

Ongoing Clinical Studies

Currently studies are underway or recruiting to assess the safety and efficacy of the use of Gardasil in females with juvenile arthritis, kidney disease, or transplant recipients. Studies are also underway to determine the safety and efficacy of the use of Gardasil in women over the age of 26.

Warnings/Precautions

Although the vaccine is shown to be close to 100% effective and may prevent cervical cancer, those who have been vaccinated should not be under the impression that Pap smears are no longer needed. This vaccine is not a substitute for getting regular check-ups and Pap smears with a healthcare provider. Routine screening for signs of cervical intraepithelial neoplasia (CIN) and other precancerous lesions will still be needed.

The health care provider should inform the patient, parent, or guardian that vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Women who receive Gardasil should continue to undergo cervical cancer screening per standard of care. Gardasil has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity. Gardasil is not intended to be used for treatment of active external genital lesions; cervical, vulvar, and vaginal cancers. Gardasil has 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 Gardasil protects only against those vulvar and vaginal cancers caused by HPV 16 and 18. Gardasil does not protect against genital diseases not caused by HPV. Vaccination with Gardasil may not result in protection in all vaccine recipients.

Adverse Reactions

On August 19, 2009, the Journal of the American Medical Association (JAMA) published an article coauthored by the FDA and the CDC that reviews the safety data for Gardasil for select adverse events that have been reported to Vaccine Adverse Event Reporting System (VAERS) – the time was from product licensure in June 2006 through December 31, 2008. The article describes 12,424 reports of adverse events following Gardasil vaccination. Of these, 772 were reports of serious events and the remaining 11,652 were classified as non-serious. During this time period, the manufacturer had distributed over 23 million doses of Gardasil in the United States.

The Gardasil safety review assessed the following adverse events: local injection site reactions, syncope, dizziness, and nausea, headaches, hypersensitivity reactions, such as rashes, hives, itching, anaphylaxis, Guillain-Barré syndrome (GBS), transverse myelitis, motor neuron disease, venous thromboembolic events (VTEs), pancreatitis, autoimmune disorders, pregnancy, and deaths. All of these events are included in Gardasil's labeling. In VAERS, a higher proportion of Gardasil reports were of syncope and VTEs compared with other vaccines. However, none of the adverse events in the safety review, including syncope and VTEs, were reported at rates greater than expected in a population of this age and gender and with other known contributing factors to these adverse events.

Concerns have been raised about reports of deaths occurring in individuals after receiving Gardasil. As of December 31, 2008, 32 deaths had been reported to VAERS. There was not a common pattern to the deaths that would suggest they were caused by the vaccine. In the majority of cases with available autopsy, death certificate and medical records, the cause of death was explained by factors other than the vaccine.

Guillain-Barre Syndrome (GBS) has also been reported in individuals following vaccination with Gardasil. GBS is a rare neurological disorder that causes muscle weakness. It occurs spontaneously in unvaccinated individuals after a variety of specific infections. To date, there is no evidence that Gardasil has increased the rate of GBS above that expected in the population. While we continue to carefully analyze all reports of GBS submitted to VAERS, the data do not currently suggest an association between Gardasil and GBS.

Based on the review of available information by FDA and CDC, Gardasil continues to be safe and effective, and its benefits continue to outweigh its risks. The CDC has not changed its recommendations for use of Gardasil. The FDA has not made any changes to the prescribing information for how the vaccine is used.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT [®] Codes	Description
90649	Human Papilloma virus (HPV) vaccine, types 6, 11, 16, 18 (quadrivalent), 3 dose schedule, for intramuscular use

ICD-9-CM Diagnosis Codes	Description
V04.89	Need for prophylactic vaccination and inoculation against certain viral diseases; other viral diseases

References

1. Centers for Disease Control and Prevention (CDC) [website]. Sexually Transmitted Diseases. Human Papillomavirus (HPV) Infection. 2004. Available at: <http://www.cdc.gov/std/hpv/default.htm>. Accessed May 24, 2006.

2. Centers for Disease Control and Prevention Advisory Committee Recommends Human Papillomavirus Virus Vaccination. Available at: <http://www.cdc.gov/od/oc/media/pressrel/r060629.htm>. Accessed on September 4, 2007.
3. Centers for Disease Control and Prevention Advisory Committee safety review of Gardasi. Available at: <http://www.cdc.gov/vaccinesafety/vaers/gardasil.htm>. Accessed September 10, 2009.
4. FDA Licenses New Vaccine for Prevention of Cervical Cancer and Other Diseases in Females Caused by Human Papillomavirus. Available at: <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01385.html>. Accessed on June 8, 2006.
5. Katz IT, Wright AA. Preventing cervical cancer in the developing world. *N Engl J Med*. 2006;354(11):1110.
6. Mao C, Koutsky LA, Ault KA, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. *Obstet Gynecol*. 2006;107(1):18-27.
7. McEvoy GK, ed. AHFS 2009 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc; 2009.
8. Medical News Today. Marketing Application For Cervarix, GSK's Candidate Vaccine For Cervical Cancer, Submitted In The European Union. March 11, 2006. Available at: <http://www.medicalnewstoday.com/medicalnews.php?newsid=39331>. Accessed May 24, 2006.
9. Merck & Co., Inc. Gardasil® (human papillomavirus (HPV) vaccine) prescribing information. Whitehouse Station, NJ: Merck & Co, Inc. October 2009.
10. Vaccine Protects Against Virus Linked to Half of All Cervical Cancers. Available at: <http://www.cancer.gov/clinicaltrials/results/cervical-cancer-vaccine1102>. Accessed on May 24, 2006.
11. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol*. 2005;6(5):271-278.

"CIGNA" and the "Tree of Life" logo are registered service marks of CIGNA Intellectual Property, Inc., licensed for use by CIGNA Corporation and its operating subsidiaries. All products and services are provided exclusively by such operating subsidiaries and not by CIGNA Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company, CIGNA Behavioral Health, Inc., Intracorp, and HMO or service company subsidiaries of CIGNA Health Corporation and CIGNA Dental Health, Inc. In Arizona, HMO plans are offered by CIGNA HealthCare of Arizona, Inc. In California, HMO plans are offered by CIGNA HealthCare of California, Inc. and Great-West Healthcare of California, Inc. In Connecticut, HMO plans are offered by CIGNA HealthCare of Connecticut, Inc. In North Carolina, HMO plans are offered by CIGNA HealthCare of North Carolina, Inc. In Virginia, HMO plans are offered by CIGNA HealthCare Mid-Atlantic, Inc. All other medical plans in these states are insured or administered by Connecticut General Life Insurance Company.

Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.