Human Papillomavirus 9-valent Vaccine (Gardasil 9®)

National Abbreviated Review Drug Monograph

October 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1-3]	
Description/ Mechanism of Action	9-valent human papillomavirus vaccine (9vHPV) is a noninfectious, virus-like particle (VLP) vaccine. Similar to quadrivalent HPV vaccine (4vHPV), 9vHPV contains HPV 6, 11, 16, and 18 VLPs. In addition, 9vHPV contains HPV 31, 33, 45, 52, and 58 VLPs.
Indication(s) under Review in this document	**9vHPV is indicated in girls and women 9 through 26 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 **9vHPV is indicated in boys 9 through 15 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 **Limitations of Use and Effectiveness:** • 9vHPV does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening or anal cancer screening if it has been recommended by a health care provider. -9 has not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity. • 9vHPV has not been demonstrated to protect against diseases due to HPV types other than 6, 11, 16, 18, 31, 33, 45, 52, and 58. • 9vHPV is not a treatment for external genital lesions; cervical, vulvar, vaginal, and anal cancers; CIN; VIN; VaIN; or AIN. • Not all vulvar, vaginal, and anal cancers are caused by HPV, and 9vHPV protects only against those vulvar, vaginal, and anal cancers

	caused by HPV 16, 18, 31, 33, 45, 52, and 58. •9vHPV does not protect against genital diseases not caused by HPV.
Dosage Form(s) Under Review	9vHPV (single dose vials and syringes)
REMS	NO REMS
Pregnancy Rating	Pregnancy Category B

Executive Summary[1-4]	
Efficacy	• The pivotal efficacy trial was conducted in women 16 to 26 years old. In this randomized trial, approximately 14,000 females had noninferior immunogenicity for the types shared by 4vHPV and 9vHPV and high efficacy for the five additional types.
Safety	• Most adverse events were injection site-related pain, swelling, and erythema that were mild to moderate in intensity.
Potential Impact	• In December 2014, the FDA approved 9vHPV. Similar to 4vHPV, 9vHPV contains HPV 6, 11, 16, and 18 VLPs. In addition, 9vHPV contains HPV 31, 33, 45, 52, and 58 VLPs. • The ACIP currently provides the same recommendation for routine use of 4vHPV and 9vHPV. Of note, 9vHPV targets five additional cancer causing types, which account for about 15% of cervical cancers. • Merck, the manufacturer for both 4vHPV and 9vHPV, state that 4vHPV will be discontinued in the future.

Background

Purpose for review The purpose of the review is to evaluate the efficacy and safety of 9vHPV

Other therapeutic options

Formulary Alternatives	Other Considerations
4vHPV	Contains HPV types 6, 11, 16, and 18; per manufacturer, 4vHPV will be replaced by 9vHPV in the future (i.e, 4vHPV will no longer be manufactured).
Non-Formulary Alternatives	**Other Considerations**
2vHPV	FDA approved only for women; ACIP only recommends for use in women

Efficacy (FDA Approved Indications)[1-8]

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to September 2015) using the search terms 9vHPV and Gardisal 9. The search was limited to studies performed in humans and published in the English language. The pivotal phase 3 clinical published in peer-reviewed journals.

Review of Efficacy

The FDA reviewed six clinical trials to support the approval of 9vHPV. The pivotal efficacy study trial was conducted in women 16 to 26 years old[4] while the pivotal immunological bridging study was conducted in boys

and girls 9 to 15 years old.[2,3] An additional immunological bridging study evaluated 4vHPV to 9vHPV in females 9 to 15 years old for HPV types 6, 11, 16, and 18.[5] These three studies were summarized by ACIP below. The remaining studies will not be discussed; two of these trials focused on concomitant administration with other vaccines[3,6] while the other evaluated safety and immunogenicity of 9vHPV in subjects previously vaccinated with 4vHPV.[7]

Summary from ACIP

In the pivotal phase III efficacy trial comparing 9vHPV with 4vHPV among approximately 14,000 females aged 16 through 26 years, 9vHPV efficacy for prevention of ≥CIN2, vulvar intraepithelial neoplasia grade 2 or 3, and vaginal intraepithelial neoplasia grade 2 or 3 caused by HPV 31, 33, 45, 52, or 58 was 96.7% in the per protocol population.[3,4] Efficacy for prevention of ≥CIN2 caused by HPV 31, 33, 45, 52, or 58 was 96.3% and for 6-month persistent infection was 96.0%.[4] Few cases were caused by HPV 6, 11, 16, or 18 in either vaccine group. Noninferior immunogenicity of 9vHPV compared with 4vHPV was used to infer efficacy for HPV 6, 11, 16, and 18. Geometric mean antibody titers (GMTs) 1 month after the third dose were noninferior for HPV 6, 11, 16, and 18; in the 9vHPV group, >99% seroconverted to all nine HPV vaccine types.

In the pivotal immunobridging trial, 9vHPV was evaluated in approximately 2,400 females and males aged 9 through 15 years with approximately 400 females aged 16 through 26 years. Over 99% seroconverted to all nine HPV vaccine types; GMTs were significantly higher in adolescents aged 9 through 15 years compared with females aged 16 through 26 years. In the other immunobridging trial, 4vHPV was compared with 9vHPV in approximately 600 adolescent females aged 9 through 15 years, 100% seroconverted to HPV 6, 11, 16, and 18 in both groups, and GMTs were noninferior in the 9vHPV group compared with the 4vHPV group.[5]

Lastly, ACIP was presented another immunogenicity trial in males aged 16 through 26 years that was compared with females of the same age group (not part of FDA original review). In both females and males, >99% seroconverted to all nine HPV vaccine types, and GMTs in males were noninferior to those in females.[2,8]

Summary of efficacy

- The pivotal efficacy trial was conducted in women 16 to 26 years old. In this randomized trial, approximately 14,000 females had noninferior immunogenicity for the types shared by 4vHPV and 9vHPV and high efficacy for the five additional types.
- ACIP ranked moderate level of evidence for among females and low level of evidence among males according to GRADE.

Potential Off-Label Use

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM intranet site only).

- At this time, 9vHPV is not FDA approved for males aged 16 through 26 years; however, ACIP reviewed additional data in this age group and has issued the same recommendations in males as 4vHPV.

Safety (for more detailed information refer to the product package insert)[1-3]

	Comments
Boxed Warning	• None
Contraindications	• Hypersensitivity including severe allergic reactions to yeast or after a previous dose of 9vHPV or 4vHPV.
Warnings/Precautions	• Syncope: To avoid fall injury, observation for 15 minutes after administration is recommended. Of note, syncope is sometimes associated with transient tonic-clonic movements and other seizure-

	like activity, which typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

Safety Considerations

Overall, 13,234 individuals received at least one dose of 9vHPV in six clinical trials. According to the CDC, the safety profiles were similar in 4vHPV and 9vHPV vaccinees. Among females aged 9 through 26 years, 9vHPV recipients had more injection-site adverse events, including swelling (40.3% in the 9vHPV group compared with 29.1% in the 4vHPV group) and erythema (34.0% in the 9vHPV group compared with 25.8% in the 4vHPV group). Males had fewer injection site adverse events. In males aged 9 through 15 years, injection site swelling and erythema in 9vHPV recipients occurred in 26.9% and 24.9%, respectively. Rates of injection-site swelling and erythema both increased following each successive dose of 9vHPV.

Adverse Reactions

Common adverse reactions	Most adverse events were injection site-related pain, swelling, and erythema that were mild to moderate in intensity.
Death/Serious adverse reactions	No deaths were reported related to 9vHPV. Five individuals that received 9vHPV experienced serious adverse event (pyrexia, allergy to vaccine, asthmatic crisis, headache, and tonsillitis) related to 9vHPV.
Discontinuations due to adverse reactions	In 2 of the studies, 0.1% participants discontinued 9vHPV due to adverse reactions.

Drug-Drug Interactions[1]

- Immunosuppressive therapies may reduce the immune response to vaccines.
- Refer to prescribing information for concomitant administration results for quadrivalent meningococcal conjugate vaccine and tetanus, diphtheria, acellular pertussis vaccine (Tdap).

Risk Evaluation

As of October 2015	Comments
Sentinel event advisories	• None with 9vHPV
Look-alike/sound-alike error potentials	• Based on clinical judgment and an evaluation of LASA information from three data sources:

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Human Papillomavirus 9-valent Vaccine, Recombinant (HPV9)	Human Papillomavirus vaccine types 6, 11, 16, 18	None	None	Human Papillomavirus vaccine types 16, 18, Recombinant(Cervarix) Humapen Humira Pen HP Acthar
Gardasil 9	Gardasil	None	None	Gynazole Vagisil Lamisil

Other Considerations[2]

CDC's ACIP Recommendations:

CDC's ACIP currently recommends routine HPV vaccination at age 11 or 12 years. ACIP also recommends vaccination for females aged 13 through 26 years and males aged 13 through 21 years not vaccinated previously.

Vaccination is also recommended through age 26 years for men who have sex with men and for immunocompromised persons (including those with HIV infection) if not vaccinated previously.

- 9vHPV, 4vHPV or 2vHPV can be used for routine vaccination of females aged 11 or 12 years and females through age 26 years who have not been vaccinated previously or who have not completed the 3-dose series. 9vHPV or 4vHPV can be used for routine vaccination of males aged 11 or 12 years and males through age 21 years who have not been vaccinated previously or who have not completed the 3-dose series. ACIP recommends either 9vHPV or 4vHPV vaccination for men who have sex with men and immunocompromised persons (including those with HIV infection) through age 26 years if not vaccinated previously.
- Refer to CDC's Supplemental information and guidance for vaccination providers regarding use of 9-valent HPV vaccine for more specific details.

Dosing and Administration[1]

Administer 9vHPV intramuscularly as a 0.5-mL dose at the following schedule: 0, 2 months, 6 months. 9vHPV should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh. Observe patients for 15 minutes after administration.

Special Populations (Adults)[1]

	Comments
Elderly	• Safety and effectiveness have not been evaluated in elderly population.
Pregnancy	• Pregnancy Category B; per PI, 9vHPV should be used during pregnancy only if clearly needed.
Lactation	• It is not known if 9vHPV is present in human breast milk; caution should be exercised.
Renal Impairment	• No data identified in prescribing information.
Hepatic Impairment	• No data identified in prescribing information.
Pharmacogenetics/genomics	• No data identified in prescribing information.

Projected Place in Therapy[1-4]

- In December 2014, the FDA approved 9vHPV. Similar to 4vHPV, 9vHPV contains HPV 6, 11, 16, and 18 VLPs. In addition, 9vHPV contains HPV 31, 33, 45, 52, and 58 VLPs.
- According to the CDC, the majority of all HPV-associated cancers are caused by HPV 16 or 18 which are targeted by all three HPV vaccines. More specifically, approximately 64% of invasive HPV-associated cancers in the United States are attributable to HPV 16 or 18 (65% for females; 63% for males; approximately 21,300 cases annually) and 10% are attributable to the five additional types in 9vHPV (14% for females; 4% for males; approximately 3,400 cases annually).
- The VHA National Center for Health Promotion and Disease Prevention's clinical guidance on HPV vaccinations state the size of VHA target population for HPV vaccination in FY 2012 is the following: 33,640 (16,788 were non-Veterans) females ages 19-26; 8,426 (6,505 were non-Veterans) males aged 19-21, and 97,644 (14,661 were non-Veterans) males ages 22-26.
- The pivotal efficacy trial was conducted in women 16 to 26 years old. In this randomized trial, approximately 14,000 females had noninferior immunogenicity for the types shared by 4vHPV and 9vHPV and high efficacy for the five additional types. Overall, adverse events were injection site-related pain, swelling, and erythema that were mild to moderate in intensity.
- The ACIP currently provides the same recommendation for routine use of 4vHPV and 9vHPV. Of note, 9vHPV targets five additional cancer causing types, which account for about 15% of cervical cancers.

References

1. Gardasil 9 [package insert]. Merck & Co, Inc, Whitehouse Station, NJ 08889, USA; December 2014.
2. Petrosky E, Bocchini JA, Hariri S, et cal. Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices. MMWR. March 2015;64:300-304.
3. FDA Vaccines, Blood & Biologics. Gardasil 9 Supporting Documents http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm426445.htm
4. Joura EA, Guiliano AR, Iversen OE , et al. Broad spectrum HPV vaccine study. A 9-valent HPV vaccine against infection and intraepithelial neoplasma in women. N Engl J Med 2015: 372:711-23.
5. Vesikari T, Brodszki N, Van Damme P, et al. A randomized, double-blind, phase III study of the immunogenicity and safety of a 9-valent human papillomavirus L1 virus-like particle vaccine (V503) vs Gardasil in 9 to 15 year old girls. *Pediatr Infect Dis J* 2015;34:992–998.
6. Schilling A, Parra MM, Gutierrez M, et al. Coadministration of a 9-valent Human Papillomavirus Vaccine with meningococcal and Tdap vaccines. Pediatrics 20151:136:563-572.
7. Garland SM, et al. Safety and immunogenicity of a 9-valent HPV vaccine in females 12–26 years of age who previously received the quadrivalent HPV vaccine. Vaccine (2015), http://dx.doi.org/10.1016/j.vaccine.2015.08.059
8. Castellsagué X, et al. Immunogenicity and safety of the 9-valent HPV vaccine in men. Vaccine (2015), http://dx.doi.org/10.1016/j.vaccine.2015.06.088

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.