



NEWS RELEASE

# FDA Approves Merck's HPV Vaccine, GARDASIL®9, to Prevent Cancers and Other Diseases Caused by Nine HPV types – Including Types that Cause About 90% of Cervical Cancer Cases

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GARDASIL 9 includes the greatest number of HPV types in any available HPV vaccine

Merck (NYSE:MRK), known as MSD outside the United States and Canada, announced today that the U.S. Food and Drug Administration (FDA) approved GARDASIL®9 (Human Papillomavirus 9-valent Vaccine, Recombinant), Merck's 9-valent human papillomavirus (HPV) vaccine, for use in girls and young women 9 to 26 years of age for the prevention of cervical, vulvar, vaginal, and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, pre-cancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, and genital warts caused by HPV types 6 and 11. GARDASIL 9 is also approved for use in boys 9 to 15 years of age for the prevention of anal cancer caused by HPV types 16, 18, 31, 33, 45, 52 and 58, precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, and genital warts caused by HPV types 6 and 11. GARDASIL 9 is contraindicated in individuals with hypersensitivity, including severe allergic reactions to yeast, or after a previous dose of GARDASIL 9 or GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant].

"With GARDASIL 9, the medical and public health community now has the potential to help prevent 90 percent of cervical cancers caused by HPV," said Dr. Julie Gerberding, president, Merck Vaccines. "This is an extraordinary opportunity to even further reduce the burden of HPV-related diseases and cancers in males and females."

GARDASIL 9 includes the greatest number of HPV types in any available HPV vaccine. After HPV types 16 and 18, the five additional HPV types in GARDASIL 9 are the most common cervical cancer-causing types worldwide. Seven HPV

types in GARDASIL 9 (HPV 16, 18, 31, 33, 45, 52 and 58) cause approximately 90 percent of cervical cancer cases and approximately 80 percent of high-grade cervical lesions (cervical precancers, defined as CIN 2, CIN 3 and AIS) worldwide. These seven HPV types also cause 85-90 percent of HPV-related vulvar cancers, 80-85 percent of HPV-related vaginal cancers, and 90-95 percent of HPV-related anal cancers. HPV types 6 and 11 cause approximately 90 percent of genital warts cases. In addition, approximately 50 percent of cases of low-grade cervical lesions (CIN 1) are caused by the nine HPV types included in the vaccine.

Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL 9 (Human Papillomavirus 9-valent Vaccine, Recombinant) protects only against those vulvar, vaginal, and anal cancers caused by HPV 16, 18, 31, 33, 45, 52 and 58.

### HPV vaccination is a public health priority in the United States

The U.S. Centers for Disease Control and Prevention (CDC) has made increasing HPV vaccination rates a public health priority. According to the CDC, HPV vaccination rates are unacceptably low compared to rates for other adolescent vaccines, and the CDC estimated that an additional 53,000 cases of cervical cancer could be prevented in girls 12 years and older over their lifetimes by increasing three-dose HPV vaccination coverage to 80 percent. The CDC has also noted that for every year that HPV vaccination rates do not improve, another 4,400 women will go on to develop cervical cancer. The CDC and other leading public health organizations, such as American Academy of Pediatrics (AAP) and National Foundation for Infectious Diseases (NFID), encourage health care providers to recommend HPV vaccine with the same sense of importance used to recommend other adolescent vaccines in order to increase vaccination rates and help protect more individuals against HPV-related cancers and other diseases. Healthy People 2020 vaccination goals of 80 percent coverage for adolescents (13 to 15 years old) are near or have been met for all routinely recommended vaccines except for HPV vaccine. Merck anticipates that the CDC's Advisory Committee on Immunization Practices (ACIP) will vote on recommendations for use of GARDASIL 9 at the February 2015 meeting.

"It's remarkable to think that we now have a vaccine designed to help prevent even more cases of cervical cancer," said Elmar Joura, M.D., associate professor of gynecology and obstetrics, Medical University of Vienna and Comprehensive Cancer Center, Vienna, Austria, and study investigator for GARDASIL 9. "GARDASIL 9 will have a significant impact in the fight against cervical, vaginal, vulvar and anal cancers."

GARDASIL 9 (Human Papillomavirus 9-valent Vaccine, Recombinant) does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Recipients of GARDASIL 9 should not discontinue anal cancer screening if it has been recommended by a health care provider.

## In clinical studies, GARDASIL 9 demonstrated high efficacy against the five additional HPV types

The clinical trial program for GARDASIL 9 was designed to build upon the efficacy established in clinical trials with GARDASIL [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]. The initial clinical program that supported the licensure of GARDASIL 9 began in 2007 and included five trials that evaluated more than 12,000 individuals who received GARDASIL 9.

The efficacy of GARDASIL 9 in 16- through 26-year-old girls and women was assessed in an active comparator-controlled, double-blind, randomized clinical trial (Study 1) that included a total of 14,204 women (GARDASIL 9 = 7,099; GARDASIL = 7,105) who were enrolled and vaccinated without pre-screening for the presence of HPV infection. Participants were followed up with a median duration of 40 months (range 0 to 64 months) after the last vaccination. The primary comparison between GARDASIL 9 and GARDASIL was clinical efficacy for the five additional HPV types. Effectiveness of GARDASIL 9 against persistent infection and disease related to the original four HPV types (6, 11, 16, or 18) was inferred from non-inferiority comparisons. The primary efficacy analysis was conducted in those who received all three doses of vaccine within one year of enrollment, did not have major deviations from the study protocol, were negative (PCR negative and seronegative) to the relevant HPV type(s) prior to dose 1, and who remained PCR negative to the relevant HPV type(s) through Month 7 (per-protocol efficacy, or PPE, population).

The primary efficacy evaluation was based on a composite clinical endpoint of HPV 31-, 33-, 45-, 52-, and 58-related cervical, vulvar, and vaginal cancer, and high-grade cervical/vulvar/vaginal disease [CIN 2/3 (cervical intraepithelial neoplasia 2/3) or AIS (adenocarcinoma in situ), VIN 2/3 (vulvar intraepithelial neoplasia 2/3), and VaIN 2/3 (vaginal intraepithelial neoplasia 2/3)]. Additional secondary endpoints related to HPV 31, 33, 45, 52, and 58 were also evaluated. Efficacy for all endpoints was measured starting after the Month 7 visit. In the PPE population, GARDASIL 9 (Human Papillomavirus 9-valent Vaccine, Recombinant) demonstrated:

- 96.7 percent efficacy (95% CI; 80.9, 99.8) against the combined incidence of cervical, vaginal, and vulvar cancers, CIN 2/3, AIS, VIN 2/3, and VaIN 2/3 caused by HPV types 31, 33, 45, 52, 58 (1 case in the group that received GARDASIL 9 vs. 30 cases in the group that received GARDASIL).
- 98.6 percent efficacy (95% CI; 92.4, 99.9) against CIN 1 caused by HPV types 31, 33, 45, 52, 58 (1 case in the group that received GARDASIL 9 vs. 69 cases in the group that received GARDASIL).
- 96.3 percent efficacy (95% CI; 79.5, 99.8) against CIN 2/3 or AIS caused by HPV types 31, 33, 45, 52, 58 (1 case in the group that received GARDASIL 9 vs. 27 cases in the group that received GARDASIL).
- 93.8 percent efficacy (95% CI; 61.5, 99.7) against vulvar or vaginal disease caused by HPV types 31, 33, 45, 52, 58 (1 case in the group that received GARDASIL 9 vs. 16 cases in the group that received GARDASIL).
- 96.2 percent efficacy (95% CI; 94.4, 97.5) against persistent HPV infection 6 months or longer with HPV types

31, 33, 45, 52, 58 (26 cases in the group that received GARDASIL 9 vs. 642 cases in the group that received GARDASIL).

- 96.1 percent efficacy (95% CI; 93.7, 97.9) against persistent HPV infection 12 months or longer with HPV types 31, 33, 45, 52, 58 (15 cases in the group that received GARDASIL 9 vs. 375 cases in the group that received GARDASIL).
- 92.6 percent efficacy (95% CI; 89.7, 94.8) against abnormal Pap tests (ASC-US HR-HPV positive or worse) caused by HPV types 31, 33, 45, 52, 58 (35 cases in the group that received GARDASIL 9 vs. 462 cases in the group that received GARDASIL).
- 96.9 percent efficacy (95% CI; 93.6, 98.6) against biopsy caused by HPV types 31, 33, 45, 52, 58 (7 cases in the group that received GARDASIL 9 vs. 222 cases in the group that received GARDASIL).
- 87.5 percent efficacy (95% CI; 65.7, 96.0) against definitive therapy related to HPV types 31, 33, 45, 52, 58 (4 cases in the group that received GARDASIL 9 vs. 32 cases in the group that received GARDASIL).

Effectiveness of GARDASIL 9 against persistent infection and disease related to HPV types 6, 11, 16, or 18 was inferred from non-inferiority comparisons of geometric mean titers (GMTs) in 16- through 26-year-old girls and women following vaccination with GARDASIL 9 with those following vaccination with GARDASIL [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]. Antibody responses for HPV 6, 11, 16, and 18 (measured by GMTs and seroconversion rates at Month 7) for GARDASIL 9 among young women 16 to 26 years of age were non-inferior to those who received GARDASIL. At least 99.7 percent of individuals included in the analysis for each HPV type became seropositive by Month 7.

### Immunogenicity of GARDASIL 9 (Human Papillomavirus 9-valent Vaccine, Recombinant)

Prior vaccination strategies have shown that the ideal time to administer a vaccine is before exposure to the infection. Immunogenicity studies for GARDASIL 9 were used for the adolescent population (9- to 15-year-old girls and boys) because adolescents are not likely to have been exposed to genital HPV types. Immunogenicity studies for GARDASIL 9 in **adolescents (9- to 15-year-olds)** are similar to that previously established and used in the clinical program for GARDASIL as a basis for licensure in this population.

Merck conducted two immunogenicity studies to support effectiveness of GARDASIL 9 in adolescents. In Study 2, effectiveness of GARDASIL 9 against persistent infection and disease related to vaccine HPV types in 9- through 15-year-old girls and boys was inferred from non-inferiority comparison of GMTs following vaccination with GARDASIL 9 among 9- to 15-year-old girls and boys with those among 16- through 26-year-old girls and women. The primary analyses were conducted in the per-protocol population, which included individuals who received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, and were HPV-naïve (seronegative to the relevant HPV type(s) prior to dose 1 and among female subjects 16 through 26 years of age, PCR negative to the relevant HPV type(s) prior to dose 1 through Month 7). In this study, anti-HPV GMTs at

Month 7 for GARDASIL 9 among 9- through 15-year-old girls and boys were non-inferior to anti-HPV GMTs among 16- through 26-year-old women for all nine HPV types.

In Study 3, effectiveness of GARDASIL 9 against persistent infection and disease related to HPV types 6, 11, 16, or 18 was inferred from non-inferiority comparisons of GMTs in 9- through 15-year-old girls following vaccination with GARDASIL 9 with those following vaccination with GARDASIL [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]. In the per-protocol population, anti-HPV 6, 11, 16, and 18 GMTs at Month 7 for GARDASIL 9 among girls 9 through 15 years of age were non-inferior to those who received GARDASIL. At least 99.7 percent of individuals included in the analyses for each HPV type became seropositive by Month 7.

Across all clinical trials with GARDASIL 9, at least 99.5 percent of individuals included in the analyses for each of the nine vaccine HPV types became seropositive by Month 7. Anti-HPV GMTs at Month 7 among 9- through 15-year-old girls and boys were comparable to anti-HPV responses among 16- through 26-year-old women in the combined database of immunogenicity studies for GARDASIL 9.

## **Safety of GARDASIL 9 (Human Papillomavirus 9-valent Vaccine, Recombinant)**

The safety of GARDASIL 9 was evaluated in six clinical studies that included more than 13,000 individuals. In clinical studies with GARDASIL 9:

- The most common ( $\geq 10\%$ ) local and systemic adverse reactions in females 16 through 26 years of age were injection-site pain (89.9%), injection-site swelling (40.0%), injection-site erythema (34.0%) and headache (14.6%).
- The most common ( $\geq 10\%$ ) local and systemic reactions in girls 9 through 15 years of age were injection-site pain (89.3%) injection-site swelling (47.8%), injection-site erythema (34.1%) and headache (11.4%).
- The most common ( $\geq 10\%$ ) local and systemic reactions in boys 9 through 15 years of age were injection-site pain (71.5%), injection-site swelling (26.9%), and injection-site erythema (24.9%).

## **Availability and CPT information for GARDASIL 9**

Merck will begin taking orders for GARDASIL 9 and begin shipping product in early February 2015. Merck anticipates that the CDC's ACIP will vote on recommendations for use of GARDASIL 9 and coverage under the Vaccines for Children (VFC) program at the February 2015 meeting. Typically, managed care coverage follows after the ACIP makes recommendations.

The American Medical Association has established a Current Procedural Terminology (CPT)® code of 906511 for GARDASIL 9. CPT codes allow for the identification and potential reimbursement of existing common procedures,

services and products' new and emerging technologies, as well as the collection of data to facilitate performance measures.

## **GARDASIL [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] continues to be available**

Because many adolescents do not visit their health care provider every year, it is important for health care providers to continue to vaccinate with GARDASIL while awaiting ACIP recommendations and managed care access for GARDASIL 9. GARDASIL is also available for males 16 to 26 years of age for whom GARDASIL 9 is not currently indicated.

## **Important Information about GARDASIL 9 (Human Papillomavirus 9-valent Vaccine, Recombinant)**

GARDASIL 9 does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening.

Recipients of GARDASIL 9 should not discontinue anal cancer screening if it has been recommended by a health care provider.

GARDASIL 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.

GARDASIL 9 has not been demonstrated to protect against diseases due to HPV types other than 6, 11, 16, 18, 31, 33, 45, 52, and 58.

GARDASIL 9 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 GARDASIL 9 protects only against those vulvar, vaginal, and anal cancers caused by HPV 16, 18, 31, 33, 45, 52 and 58.

Vaccination with GARDASIL 9 may not result in protection in all vaccine recipients.

## **Select Safety Information for GARDASIL 9**

GARDASIL 9 is contraindicated in individuals with hypersensitivity, including severe allergic reactions to yeast, or after a previous dose of GARDASIL 9 or GARDASIL [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18)

Vaccine, Recombinant].

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 HPV vaccination. 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.

### Dosage and administration for GARDASIL 9 (Human Papillomavirus 9-valent Vaccine, Recombinant)

GARDASIL 9 should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh at the following schedule: 0, 2 months, 6 months.

### About HPV and related cancers and diseases

Human papillomavirus (HPV) causes virtually all cervical cancer cases. HPV also causes approximately 70-75 percent of vaginal cancer cases and approximately 30 percent of vulvar cancer cases in females, and approximately 85-90 percent of anal cancers and genital warts in both females and males. Approximately 575,000 cases of these HPV-related cancers occur annually worldwide. Millions of cases of genital warts occur worldwide each year in females and males.

Each day, another 33 women are diagnosed with cervical cancer in the United States -- about 12,000 women per year. Additionally, there are an estimated 2.8 million abnormal Pap results, many of which are caused by HPV, that require follow-up each year in the United States.

Anal cancer and genital warts affect both men and women. According to the American Cancer Society, it is estimated that approximately 2,600 men and 4,500 women in the United States will be diagnosed with anal cancer in 2014. There is no routine screening recommended for the general population to reduce the risk of anal cancer. Approximately one million cases of genital warts occur each year in the United States. Treatment of genital warts can be painful, and they commonly recur after treatment, especially in the first three months.

### About Merck

Today's Merck is a global healthcare leader working to help the world be well. Merck is known as MSD outside the United States and Canada. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions.

We also demonstrate our commitment to increasing access to healthcare through far-reaching policies, programs and partnerships. For more information, visit **www.merck.com** and connect with us on **Twitter**, **Facebook** and **YouTube**.

## Forward-Looking Statement

This news release includes "forward-looking statements" within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of Merck's management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; Merck's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of Merck's patents and other protections for innovative products; the exposure to litigation, including patent litigation, and/or regulatory actions.

Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in Merck's 2013 Annual Report on Form 10-K and the company's other filings with the SEC available at the SEC's Internet site (**www.sec.gov**).

Please see Prescribing Information for GARDASIL®9 (Human Papillomavirus 9-valent Vaccine, Recombinant) at [http://www.merck.com/product/usa/pi\\_circulars/g/gardasil\\_9/gardasil\\_9\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf). The Patient Product Information for GARDASIL 9 is also available at [http://www.merck.com/product/usa/pi\\_circulars/g/gardasil\\_9/gardasil\\_9\\_ppi.pdf](http://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_ppi.pdf).

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Medical Association. CPT codes are effective as of January 2015 as set forth in the Current Procedural Terminology 2015.

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