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Gardasil® Update: New Indications and Postmarketing Surveillance by Lisa Garrity, PharmD

Introduction: Gardasil®, the recombinant human papillomavirus (HPV) vaccine approved for use in 2006, was introduced in the November/December 2006 edition of *Pharmacotherapy Update*. This article will provide updates on immunization recommendations for HPV vaccination and recently updated indications for use approved by the Food and Drug Administration (FDA). Additionally, frequently asked questions regarding Gardasil® will be covered, including administration of the vaccine and reported adverse events.

HPV Background and Risk: Human papillomavirus is the most common sexually transmitted infection (STI) in the United States. Nearly 6.2 million Americans are infected with HPV each year, with nearly 20 million between the ages of 15 and 49 years.¹ Sexually active persons between the ages of 15 and 24 years comprise nearly half of those infected with HPV. The highest rates of infection occur among sexually active young women, with an incidence of 40% by 24 months after the first occurrence of sexual intercourse.²

Most HPV infections are transient, with 90% resolving within 2 years without sequelae. Persistent HPV infections are associated with genital warts in men and women, as well as risk for developing precancerous lesions that may progress to cervical cancer in women. Cervical cancer is the second most common type

of cancer in women worldwide, resulting in over 200,000 deaths annually.² HPV has been detected in 99.7% of cervical cancers and has been associated with vaginal, vulvar, anal, penile and perianal cancer. There are over 100 different types of HPV identified, with approximately 18 types determined to be oncogenic. HPV types 16 and 18 cause approximately 50% and 20% of cervical cancers, respectively. Although benign, genital warts are another troublesome outcome of HPV infection, with HPV types 6 and 11 associated with 90% of cases.^{2,3}

No effective systemic treatments are available for individuals infected with HPV. Use of physical barriers such as condoms decrease the HPV transmission rate, but do not eliminate the risk of transmission completely.³ Abstaining from intercourse or limiting the number of sexual partners has been shown to decrease risk of HPV infection. The introduction of the HPV vaccine has provided another means of prevention for young women.

Gardasil® Vaccine: Quadrivalent recombinant human papilloma (types 6, 11, 16, 18) virus vaccine (Gardasil®) was approved for use in 2006. The vaccine targets the four HPV types most associated with cervical cancer and genital warts. Indications for use include prevention of

Table 1: Gardasil® Indications for Use⁴

Indicated for use in prevention of the following cancers and precancerous lesions:
Cervical, vulvar, or vaginal cancer caused by HPV types 16 and 18
Genital warts caused by HPV types 6 and 11
Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS)
CIN grade 1
Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3

cervical cancer, genital warts, and neoplasias caused by HPV types included in the vaccine in women 13 to 26 years of age (see Table 1).⁴ Indications for prevention of vaginal and vulvar cancer with Gardasil® were approved by the FDA in September 2008. Currently, Gardasil® is not approved for use in males or women over 26 years of age.⁴

Efficacy: Clinical studies have shown Gardasil® is highly effective in preventing persistent HPV infections associated with HPV types 6, 11, 16 and 18.⁵⁻⁷ In placebo-controlled phase III clinical trials [Females United to Unilaterally Reduce Endo/Ectocervical Disease, (FUTURE I and FUTURE II)] involving over 20,000 women, the three dose vaccination regimen of quadrivalent HPV vaccine was 96% effective in preventing persistent HPV infections associated with these types.^{5,6} The efficacy of Gardasil® for prevention of HPV-type 16 and HPV-type 18 related precancerous lesions in FUTURE II was 98%, with 100% efficacy for prevention of vulvar and vaginal intraepithelial neoplasias and genital warts for HPV genotypes covered by the vaccine.⁷

It is important to note that Gardasil® does not protect against all HPV types that may cause cervical cancer. Women receiving the vaccination should continue to receive Pap smears every 2 to 3 years to screen for cervical cancer. Gardasil® will not provide protection in women that have already been infected with HPV and cannot be used to treat active cervical, vulvar, or vaginal cancer or active cases of genital warts. Gardasil® will only protect against vulvar or vaginal cancers caused by HPV.⁴

Contraindications: Contraindications to use of Gardasil® include hypersensitivity to yeast or severe allergic reactions to previous doses of Gardasil®. Patients receiving immunosuppressive medications may have a diminished immune response to vaccines, including Gardasil®.⁴

Dosing and Administration: Gardasil® is administered as a series of three intramuscular injections given at day 0, month 2, and month 6. There is no maximal time period between vaccinations in the series. If patients are off-schedule or have not completed the series, remaining HPV doses can be given following the recommended schedule, with the second dose given as soon as possible and an interval of at least 12 weeks between the second and third dose. Doses are given in the deltoid muscle, since other sites of administration have not been studied. Because of a risk for syncope or fainting, particularly in young adolescent females, patients should be observed for 15 minutes after receiving a dose of Gardasil®. Vaccine Information Statements are required to be given with each vaccination to the patient, parent, or guardian [Available at: www.cdc.gov/vaccines/pubs/vis/default.htm].

Gardasil® is supplied as 0.5 ml suspension for intramuscular injection in single dose vials or prefilled syringes. Syringes and vials should be refrigerated and protected from light. Once removed from refrigeration, Gardasil® should be administered as soon as possible. Gardasil® should not be used if kept at room temperature for more than 72 hours.⁴

Concurrent administration of Gardasil® with other vaccines has not been evaluated, with the exception of the hepatitis B vaccine (Recombivax HB®), where no loss of efficacy for either vaccine was observed with co-administration.⁴ A clinical trial studying co-administration of Gardasil® with Tdap is ongoing.⁸ Since Gardasil® is an inactivated virus, no problems are anticipated from co-administration with other scheduled vaccines. Vaccinations should be administered in different sites using different syringes.⁴ The Advisory Committee on Immunization Practices (ACIP) recommends co-administration of vaccines to improve the likelihood that adolescents receive all required vaccinations.⁹

Table 2: Cervical Cancer Screening Guidelines in the United States

Guidelines	American Cancer Society ¹¹	US Preventive Services Task Force ¹²	American College of Obstetricians and Gynecologists ¹³
Start screening	3 years after onset of vaginal intercourse, no later than age 21 years	Within 3 years of onset of sexual activity or age 21 years	3 years after onset of sexual intercourse, no later than age 21 years
Intervals for screening			
Conventional Pap test	Annually age <30 years; every 2-3 years women aged ≥30 years with three negative cytology tests	At least every 3 years	Annually age <30 years; every 2-3 years women aged ≥30 years with three negative cytology tests
Liquid-based cytology	Every 2 years age <30 years; every 2-3 years women aged ≥30 years with three negative cytology tests	Insufficient evidence	Annually age <30 years; every 2-3 years women aged ≥30 years with three negative cytology tests
HPV testing as adjunct to cytology	Every 3 years if HPV negative, cytology negative	Insufficient evidence	Every 3 years if HPV negative, cytology negative

Adapted from MMWR Morb Mortal Wkly Rep 2008;56(RR-2):1-24.

Women receiving the HPV vaccine should continue to be screened for cervical cancer, since only the two strains responsible for 70% of cervical cancers are targeted by Gardasil[®].⁴ Vaccinated females could be infected with other carcinogenic strains of HPV and may have been infected with HPV prior to vaccination. Screening guidelines for cervical cancer in the United States recommended by the American Cancer Society, US Preventative Health Services Task Force and American College of Obstetricians and Gynecologists are listed in Table 2.¹¹⁻¹³ Data available for vaccination coverage in adolescents age 13 to 17 years showed 25.1% of females in this age group initiated the HPV series in 2007.¹⁴

Pregnancy and Lactation: Gardasil[®] is classified as pregnancy-risk category B and is not recommended for use in pregnant women since no adequate and well-controlled studies in pregnant women have been conducted.⁴ Initiation of the HPV vaccine sequence should be delayed if females are pregnant, and if women have already started the series, any remaining doses in the regimen should be delayed until pregnancy completion. Lactating women can receive the HPV vaccine.⁴ Merck, the manufacturer of Gardasil[®], has a pregnancy registry in place for patients that are administered the HPV vaccine while pregnant to monitor maternal and fetal outcomes. Physicians are encouraged to make reports to the registry for any inadvertent pregnancy exposures to Gardasil[®] by contacting Merck at 1-800-986-8999.

The second annual report from the Gardasil[®] Pregnancy Registry for the period from June 1, 2006 through May 31, 2008, reported 2,149 reports of exposure to the HPV vaccine during pregnancy. Of these reports, 787 were prospective, while 76 were retrospective, with separate analyses used. For the prospective reports, outcomes of 491 pregnancies were reported, with 140 lost to follow-up, 130 pending and 26 elective abortions. Of the 491 reports, 451 live births occurred with 34 reports of spontaneous abortion and seven fetal deaths (one twin pregnancy resulted in a live birth and a fetal death and is recorded twice in these outcomes). Regarding infant outcomes, of 454 newborns, 439 were normal infants, 14 were born with congenital anomalies and one early neonatal death occurred. Four of these reports did not meet criteria for classification as a major anomaly. Of the 76 retrospective reports of exposure, seven elective abortions and 19 spontaneous abortions were recorded, as well as two ectopic pregnancies, four reports of fetal death, and 44 live births. This information indicates that occurrence of spontaneous abortions and fetal death for women receiving Gardasil[®] does not exceed the background rates for these events. Congenital anomalies reported to the registry were varied in gestational age, type, and etiology, thus suggesting that HPV vaccination is unlikely to contribute to adverse pregnancy outcomes.¹⁵

Adverse Reactions: Although exact numbers are unavailable regarding the overall number of HPV vaccinations administered, over 20 million doses of Gardasil[®] have been distributed in the United States.¹⁶ Of all adverse events from Gardasil[®] reported to the Vaccine Adverse Events Reporting System (VAERS), 94% were classified as non-serious and most commonly included headache, pain at the injection site, nausea, fever, swelling, bruising, erythema, pruritis, dizziness, and syncope. Serious adverse events that have been reported include blood clots, Guillain-Barré Syndrome (GBS), and death. Patients with reported blood clots generally had other risk factors, including use of oral contraceptives.¹⁷

Guillain-Barré Syndrome, a rare but serious neurological disease of unknown cause, is reported in 1 to 2 of every 100,000 person-years during the second decade of life. As of August 31, 2008, 52 reports of GBS after Gardasil[®] vaccination were entered into the VAERS database, with 13 of the 52 reports confirmed GBS cases. Of these cases, nine occurred within 4 to 42 days after Gardasil[®] administration. Co-administration of the meningococcal vaccine, Menactra[®], was reported for 6 of 13 cases. Of the remaining VAERS reports, 11 did not meet the definition for GBS, one had symptoms prior, 12 did not have sufficient information, and 15 cases are pending follow-up. Given the background rate of GBS occurrence, GBS reported for Gardasil[®] administration is low, particularly compared to other vaccines.^{16,18}

As of August 31, 2008, 27 deaths following Gardasil[®] administration were reported to the Centers for Disease Control and Prevention (CDC). Deaths included all-cause mortality and were based on event reports; non-vaccine causes of death were listed for nearly all of the cases reported to the database. Deaths occurred from as little as 2 days to several months after vaccine administration.^{4,17} Information provided by Merck in Gardasil[®] product labeling noted across all clinical trials, 24 deaths were reported out of 25,274 subjects (Gardasil[®] and control, ages 9 to 45 years for females and 9 to 15 years for males). The most common causes of death were motor vehicle accident (four in Gardasil[®] group, three in control group), overdose/suicide (two each in Gardasil[®] and control groups) and pulmonary embolus/deep vein thrombosis (one each in Gardasil[®] and control groups).⁴

Vaccine Safety Reporting: VAERS is a postmarketing safety surveillance program for all licensed vaccines in the United States managed by the CDC and FDA. Adverse events occurring after or that are suspected to be related to any type of vaccination such as Gardasil[®] should be reported and all serious adverse reactions to vaccination must be reported. Reports can be made by patients, parents, health care providers, and vaccine manufacturers to VAERS online at www.vaers.hhs.gov, by telephone at (800) 822-7967, or by mail.

Controversies Surrounding Gardasil[®]: Several controversies regarding Gardasil[®] have arisen since the vaccine was introduced. The vaccine is indicated for use in adolescent girls, with recommendations that the series be administered around 11 to 12 years of age, and as early as 9 years.⁹ Several groups have voiced concern that sexual activity among adolescents will increase after the HPV vaccination is given, and legislation has arisen as attempts have been made to introduce mandatory HPV vaccination. Judicial Watch, a group opposing mandatory HPV vaccination in adolescents, provides information and opinion on Gardasil[®] at www.judicialwatch.org.

Another source of controversy arises from fear of adverse events after vaccination. Patients searching for information on the Gardasil[®] vaccine may find sources that report thousands of serious adverse reactions and many deaths occurring after use of the Gardasil[®] vaccine. Websites where patients may obtain opinion articles and information opposing vaccinations include www.mercola.com, a site run by Dr. Joseph Mercola, an osteopathic physician promoting herbal remedies for most conditions, and the National Vaccine Information Center (NVIC), www.nvic.org, a consumer organization promoting individual choice in receiving vaccinations.

The long-term effects of Gardasil[®] are not currently known. Clinical trials used for approval of Gardasil[®] by the FDA used surrogate endpoints for efficacy of the vaccine against cervical, vaginal, and vulvar cancer, and the presence of potentially precancerous lesions.⁵⁻⁷ The effects of Gardasil[®] on development of cervical, vaginal, and vulvar cancer have not been studied. The duration of efficacy for Gardasil[®] is also unknown. Studies of Cervarix[®], a bivalent HPV vaccine against HPV types 16 and 18, demonstrated that high rates of seropositivity (~98%) were maintained 4.5 years after completion of a three-dose vaccination series.¹⁹ It is not yet known if booster vaccinations of Gardasil[®] will be needed to maintain protection against HPV.

In the Pipeline: Published clinical trials have shown efficacy of Gardasil[®] in adolescent males.²⁰ Clinical trials are also ongoing to study vaccination in preadolescents ages 10 to 12 years.⁸ GlaxoSmithKline has a bivalent HPV (types 16 and 18) vaccine, Cervarix[®], not yet approved for use in the United States but currently under investigation in Phase III clinical trials. Cervarix[®] is already approved for use in Europe, Japan, Canada and other countries.⁸

Cleveland Clinic Formulary: Gardasil[®] was added to the Cleveland Clinic Formulary in 2006 for use in patients meeting the FDA-approved age requirements. It is restricted to outpatient use only for adults, but can be given to pediatric patients in the inpatient or outpatient settings.

Cost: The cost of the three dose series of Gardasil[®] is approximately \$360.²¹

Conclusion: Gardasil[®], the quadrivalent HPV vaccine providing protection against HPV types 6, 11, 16, and 18, provides high levels of protection against HPV-type 16 and HPV-type 18 associated cervical, vaginal, and vulvar cancers and genital warts. Gardasil[®] appears to be safe and well-tolerated, with reported adverse event rates similar to those of other vaccines currently available. However, many controversies regarding HPV vaccination exist which prevent widespread acceptance of the vaccine. Information regarding long-term safety and efficacy for the HPV vaccine is not yet available. No changes to CDC recommendations regarding Gardasil[®] have been made since publication in March 2007, and surveillance of adverse effects of the HPV vaccine are ongoing through the VAERS reporting system.

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Did You Know....

Lacosamide (Vimpat®)

by Chris Madjerich, Pharm.D. Candidate

Lacosamide (Vimpat®, UCB, Inc.) is a new antiepileptic medication that is FDA-approved as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older. Although the exact mechanism of action for lacosamide is not completely understood, *in vitro* studies show that it selectively enhances slow inactivation of voltage-gated sodium channels with no effect on fast inactivation of sodium channels. This effect on slow sodium channels results in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing. This mechanism is different from other frequently used antiepileptic medications used for partial-onset seizures.

The oral bioavailability of lacosamide is near 100%, and it is less than 15% bound to plasma proteins. Lacosamide is metabolized in the liver via the cytochrome P450 (CYP) 2C19 isoenzyme and is excreted by the kidneys. The most common adverse effects reported with lacosamide are dizziness (31%), headache (13%), diplopia (11%), nausea (11%), fatigue (9%), vomiting (9%), and blurred vision (8%). It is important to note that lacosamide may increase the risk of suicidal thoughts or behavior, and it is recommended to monitor patients for changes in behavior. It is also advised for patients to avoid alcohol while being treated with lacosamide because this can increase the risk of dizziness and drowsiness. There have been reports of asymptomatic first-degree atrioventricular block in patients using lacosamide and caution should be used when giving lacosamide with other medications that may prolong the PR interval (e.g., beta blockers, antiarrhythmics). The use of lacosamide in pregnancy has not been studied in humans; however, it has been shown to cross the placenta and enter breast milk in animal studies. Lacosamide is classified as a pregnancy-risk category C.

The adult dose of lacosamide should be titrated beginning with 50 mg (oral or intravenous) given twice daily and increased in weekly intervals by 100 mg/day. The recommended daily dosage is 200 to 400 mg/day based on patient response, and it should be given twice daily in equally divided doses. In patients with severe renal impairment (CrCl <30 mL/min) or mild to moderate hepatic impairment, the maximum daily dose is 300 mg/day. Lacosamide use is not recommended in patients with severe hepatic impairment. When discontinuing therapy, lacosamide should be withdrawn gradually to minimize the potential of increased seizure frequency. Lacosamide is available in oral tablets (50-, 100-, 150- and 200-mg) and in an intravenous solution (200 mg/20 mL). When switching from intravenous to oral administration, it should be done at equivalent doses and dosing intervals. It is important to note that lacosamide is classified as a controlled substance (C-V) because in a human abuse potential study, it produced euphoric-type responses that were indistinguishable from those produced by alprazolam. Lacosamide oral tablets are on the Cleveland Clinic Formulary. Lacosamide intravenous solution is on the Formulary, but its use is restricted to pediatric patients. The average wholesale price (AWP) for the tablets varies: \$4.30 per 50 mg tablet and ranges from \$6.70 to \$7.55 for the 100-, 150-, and 200-mg tablets.

Due to its unique mechanism of action, lacosamide offers another therapeutic option for patients with partial-onset seizures that are not adequately controlled on other antiepileptic therapy.

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