Panel Backs Vaccine for Genital Warts in Boys

BY ELIZABETH MECHCATIE

SILVER SPRING, MD. — In nearly unanimous votes, a Food and Drug Administration advisory panel agreed that data on Gardasil supported the efficacy and safety of the vaccine for use in preventing genital warts caused by human papillomavirus types 6 and 11 in boys and men aged 9-26 years.

The FDA's Vaccines and Related Biological Products Advisory Committee voted 7-0 with 1 abstention on the efficacy question and voted 7-1 on the safety question. The panel was not asked specifically whether to recommend licensure of Gardasil (human papillomavirus [types 6, 11, 16, 18] recombinant vaccine), manufactured by Merck & Co. The FDA usually follows the recommendations of its advisory panels. The company expects the FDA to make a decision during the fall season, according to a Merck spokesperson.

The vaccine is licensed for use in girls and women aged 9-26 years, for the prevention of cervical, vulvar, and vaginal cancer caused by the oncogenic HPV types 16 and 18, and associated precursor dysplastic lesions (CIN, VaIN, AIS), and genital warts caused by HPV 6 and 11. It has been available since 2006 and is administered in a three-dose series of intramuscular injections at 0, 2, and 6 months.

The expanded indication proposed by Merck is for use in boys and men aged 9-26 years of age, "for the prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11," the two HPV types that cause the majority of genital warts.

Gardasil was evaluated in a pivotal safety and efficacy study, a multinational study of approximately 4,000 boys and men aged 16-26 years, who received Gardasil or placebo; 85% were heterosexual and 15% were men having sex with men. (Almost 30% of the participants were in North America.) Participants with a history of genital warts, no history of sexual activity, and those with more than five lifetime sexual partners were excluded.

The primary end point was the effect of the vaccine on the combined incidence of HPV 6/11/16/18–related external genital lesions (EGL), which included external genital warts, penile/perianal/perineal intraepithelial neoplasia (PIN), and penile, perianal, or perineal cancer. Approximately 1,800 of the subjects in the study met the protocol, and received all three Gardasil doses and were tested at month 7. In this group, the vaccine was 90% effective in preventing HPV 6/11/16/18–related EGL, a highly statistically significant effect. Most of the effect was on condylomata acuminata, the focus of the proposed indication: The vaccine was 89% effective in preventing condylomata acuminata. There were few cases of PIN and no cases of cancer in either placebo or Gardasil recipients.

An "immunobridging" study of adolescent boys (aged 9-15 years) and boys and men aged 16-26 years, who received the three Gardasil doses, determined that the immune responses to each of the four HPV types among the younger participants were not inferior to the responses seen among those in the older group. These results "inferred" efficacy of the vaccine in 9- to 15-year-olds, according to Merck.

In the pivotal trial, adverse events reported 1-15 days after any of the vaccinations, was 10% higher (74% vs. 64%) among Gardasil recipients, mostly because of injection site–related adverse events (the most common was injection-site pain). Systemic adverse events were slightly higher in the vaccine group; no serious adverse events were attributed to the vaccine. More than 95% of the adverse events were mild to moderate.

In the safety database of about 5,400

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boys and men, no safety signals have been identified, according to the FDA. There were no reports of syncope, which has been reported among female recipients since Gardasil was approved.

Merck is planning postlicensure studies that will continue to assess the safety and efficacy of Gardasil in males, including a 10-year follow-up of long-term safety, efficacy, and immunogenicity in the extension of the pivotal study and the immunobridging study of 9- to 15-year-olds, and a safety study using an HMO database, of about 27,000 boys and men who receive at least one dose of Gardasil.

Pamela McInnes, D.D.S., director of the division of extramural research at the National Institute of Dental and Craniofacial Research, Bethesda, Md., who voted in favor of safety and efficacy, said that duration of immunity is a "critical issue" that needs to be studied to determine whether a booster will be necessary for lifelong protection.

No serious adverse events were attributed to the HPV vaccine. More than 95% of the adverse events were mild to moderate in nature.

The consumer representative on the panel, Vicky Debold, Ph.D., R.N., director of patient safety at the National Vaccine Information Center, Vienna, Va., voted no on the safety question, and abstained on the efficacy question. More information about safety in girls is needed "before we subject boys to this," she said, referring to a recent review of postmarketing reports of postvaccination thromboembolic events and syncope in JAMA (2009; 302:750-7).

In that study of postvaccine problems reported to the Vaccine Adverse Events Reporting System (VAERS) over a 2.4-year period, reports of syncope and venous thromboembolism after vaccination with Gardasil exceeded the expected background rates. The company responded that Gardasil has not been associated with an increase in thromboembolic events, and that the events reported have been in people with risk factors for thromboembolism. ■

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