NEW SHINGLES VACCINE EARNS FDA PANEL NOD

Shingrix shows 91.3% efficacy in seniors

BY KARI OAKES

A new vaccine is both safe and effective in preventing herpes zoster, and in reducing the incidence of postherpetic neuralgia in older adults, according to a Food and Drug Administration advisory committee, which voted unanimously to recommend the vaccine.

The FDA generally follows the recommendations of its advisory committees.

The recombinant vaccine, dubbed HZ/su during the trial phase, showed efficacy of 97.2% against herpes zoster infection in adults aged 50 years and older, and 91.3% in adults aged 70 years and older. The effect persisted for up to the 4 years of study follow-up.

GlaxoSmithKline plans to market the vaccine as Shingrix, to be administered to adults aged 50 years and older.

HZ/su had a generally favorable safety profile, though early constitutional symptoms and local site reactions were common, according to data presented by GlaxoSmithKline. HZ/su uses an adjuvant not found in any other U.S.-approved vaccine.

The incidence of postherpetic neuralgia, a common, persistent, and costly complication of herpes zoster, was 0.1 per 1,000 person-years in those receiving vaccine, compared with 0.9-1.2 per 1,000 person-years for those receiving placbo

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tained efficacy seen for HZ/su in the trial data, especially for older populations. However, some participants wondered about the generalizability of both safety and efficacy data to all populations, given the very low trial enrollment numbers for Africans, African Americans, and individuals of Hispanic origin.

The two studies, Zoster-006 and Zoster-022, were similar in design and were conducted in parallel across 18 countries; data were able to be pooled for key efficacy and safety outcomes. Study Zoster-006 enrolled patients aged 50 years and older, while study Zoster-022 began enrollment at age 70. Patients were randomized to receive vaccine or placebo, and were followed for a median of 3.1 years for efficacy in Zoster-006 and a median of 3.9 years for Zoster-022. Safety data were obtained for a median 4.4 years for both studies.

The primary outcome measure for both studies in pooled analysis was the vaccine's effectiveness against herpes zoster and postherpetic neuropathy in adults aged 70 and over. Safety was also assessed using pooled data.

The United States was represented by 3,934 of more than 29,000 patients enrolled globally. The remainder were primarily in Western Europe, with some sites in Australia and eastern Asia, Canada, and Latin America.

The vaccine consists of a recombinant, lyophilized truncated form of the varicella zoster virus (VZV) in the pivotal clinical trials for a median follow-up of 4 years.

In the vaccine's pivotal clinical trials, efficacy was significantly higher than the levels seen for the only currently approved zoster live vaccine, Zostavax, especially for older populations. Zostavax's efficacy for those aged 50-59 years is 69.8%, dropping to 18% for those aged 80 years or older.

The results of the two pivotal clinical trials were presented and analyzed by the sponsor and by FDA staff during a meeting of the Vaccines and Related Biological Products Advisory Committee of the FDA's Center for Biologics Evaluation and Research (CBER).

During pre-vote discussions, committee members were unanimous in noting with favor the high and sus-

transient innate response in the first 3 days after administration that later helps maintain durably high levels of gE-specific antibodies and strengthens gE-specific cell-mediated immunity.

Mechanistically, the robust initial innate response is responsible for the constitutional symptoms and local site reactions seen in pooled data from the two pivotal clinical trials: 70%-85% of participants receiving HZ/su reported injection-site pain, 38% of participants receiving HZ/su reported redness, and about a quarter reported swelling.

By comparison, 9%-13% of those receiving placebo reported injection-site pain, and about 1% reported redness and swelling.

Fatigue, headache, mild fever, myalgia, and shivering were all more common in those receiving HZ/su; both local and generalized symptoms were more common in younger recipients.

"I think this is a very good case for the first licensure of this adjuvant in the United States, because the efficacy seems pretty compelling, the disease is morbid, and there are a lot of people whose lives would be changed," said committee member Sarah Long, MD, professor of pediatrics at Drexel University, Philadelphia.

Both the GSK and FDA presentations were in agreement that serious adverse events were in the range to be expected for an older population, and balanced across study arms.

glycoprotein E (gE) antigen protein that, at the time of administration, is reconstituted with a novel adjuvant suspension. The antigen selection was based on the fact that gE is expressed on the surface of infected cells and is the target of both humoral and cellular immune responses in the host, said GSK's Arnaud Didierlaurent, PhD, director and head of the adjuvant platform for GSK Vaccine's Belgium research and development division.

The adjuvant, termed ASO1B, is not currently in use for any U.S.-approved vaccine, though it was developed more than 20 years ago, said Dr. Didierlaurent. Its combination with recombinant VZV gE was found to significantly boost the antigen's immunogenicity during GSK's vaccine development program. The adjuvant enhances a

However, particular attention will be given to certain potential complications during the proposed pharmacovigilance plan.

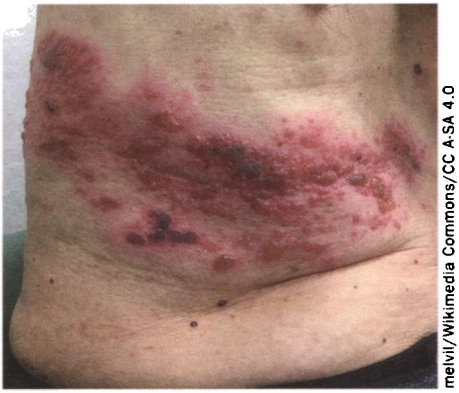
"An imbalance toward vaccine versus placebo was observed" for gout, optic ischemic neuropathy, amyotrophic lateral sclerosis, osteonecrosis, convulsion-type reactions, and supraventricular tachycardias. "All are an adverse event of interest and will be included in planned targeted safety study," said Dr. Didierlaurent.

Several committee members remarked on the difficulty of evaluating vaccine safety in an older population, where analysis takes place against the backdrop of more comorbidities and acute illnesses than in the younger population.

"There has been a thoughtful job both by the sponsor and by CBER in looking at complicated data," said Melinda Wharton, MD, the director of the immunization services division of the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention, Atlanta.

The committee's chair, Kathryn Edwards, MD, agreed. "I applaud the comprehensive analysis of all these safety signals. Both the sponsor and the FDA have done a wonderful job of drilling down and answering these questions," she said. Dr. Edwards is the Sarah H. Sell and Cornelius Vanderbilt chair in pediatrics at Vanderbilt University, Nashville, Tenn.

Herpes zoster, a reactivation of the varicella virus that lies dormant in dorsal root or cranial nerve ganglia from earlier infection, is seen in about 1 million cases per year in the United States, with about 100,000-200,000 cases of postherpetic neuralgia occurring, said Jeffrey Cohen, MD, chief of the laboratory of infectious diseases at the National Institute of Allergy and Infectious Diseases, Bethesda, Md. The rates of herpes zoster are increasing in the United States for unknown reasons, and direct medical costs may currently exceed $1 billion annually, he said.



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Each 0.5-mL dose of the HZ/su vaccine contains 50 mcg each of the recombinant VZV gE antigen and each of the two component parts of the ASO1B adjuvant. Two doses of the vaccine are administered intramuscularly 2-6 months apart. Dose-ranging studies were conducted before the pivotal clinical trials to ascertain the optimal dose of all of the vaccine components, the need for two doses, and the optimal spacing between doses.

All committee participants submitted conflict of interest statements to the FDA, and any potential conflicts were resolved before the hearing.

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