State of California—Health and Human Services Agency
California Department of Public Health

KAREN L. SMITH, MD, MPH
Director and State Public Health Officer

EDMUND G. BROWN JR.
Governor

7/12/2018 Update: Note page 3 correction for RZV's VFA eligibility age.

July 10, 2018 IZB-FY-18-19-1

TO: Vaccines for Adults (VFA) Providers

FROM: Sarah Royce, M.D., M.P.H., Chief
Center for Infectious Diseases
Division of Communicable Disease Control, Immunization Branch

SUBJECT: SHINGRIX® (Zoster Vaccine Recombinant, Adjuvanted; RZV) IS NOW AVAILABLE FROM VFA

SUMMARY

On October 20, 2017, the United States (U.S.) Food and Drug Administration (FDA) licensed Zoster Vaccine Recombinant, Adjuvanted (Shingrix®, GlaxoSmithKline [GSK], Research Triangle Park, North Carolina) for use in adults ages 50 years and older. Shingrix® is a two-dose vaccine containing recombinant glycoprotein E in combination with a novel adjuvant ($AS01_B$), indicated for the prevention of herpes zoster (shingles). On October 25, 2017, the Advisory Committee on Immunization Practices (ACIP) recommended the recombinant zoster vaccine (RZV) for use in immunocompetent adults ages 50 years and older, and in preference to the existing Zoster Vaccine Live (ZVL, Zostavax®), for the prevention of herpes zoster and related complications. The California Department of Public Health,

Immunization Branch concurs with ACIP's recommendations for the preferential use of the new recombinant Zoster vaccine, Shingrix®. This letter summarizes information about the use of RZV.

BACKGROUND AND COMPOSITION

Herpes zoster is a localized, usually painful, cutaneous eruption resulting from reactivation of latent varicella zoster virus (VZV). Herpes zoster is common: approximately one million cases occur each year in the United States. The incidence increases with age, from five cases per 1,000 population in adults aged 50-59 years to 11 cases per 1,000 population in persons aged 80 years and older. Postherpetic neuralgia, commonly defined as persistent pain for at least 90 days following the resolution of the herpes zoster rash, is the most common complication and occurs in 10%-13% of herpes zoster cases in persons over age 50; the risk for developing postherpetic neuralgia also increases with age.

Shingrix® (Zoster Vaccine Recombinant, Adjuvanted) is a sterile suspension for intramuscular injection. The vaccine is supplied as a vial of lyophilized recombinant varicella zoster virus surface glycoprotein E (gE) antigen component, which must be reconstituted at the time of use with the accompanying vial of $AS01_B$ adjuvant suspension component. The lyophilized gE antigen component is presented in the form of a sterile white powder. The $AS01_B$ adjuvant suspension component is an opalescent, colorless to pale brownish liquid supplied in vials.

The gE antigen is obtained by culturing genetically engineered Chinese Hamster Ovary cells, which carry a truncated gE gene, in media containing amino acids, with no albumin, antibiotics, or animal-derived proteins. The gE protein is purified by several chromatographic steps, formulated with excipients, filled into vials, and lyophilized.

The adjuvant suspension component is $AS01_B$ which is composed of 3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* and QS-21, a saponin purified from plant extract *Quillaja saponaria Molina*, combined in a liposomal formulation. The liposomes are composed of dioleoyl phosphatidylcholine (DOPC) and cholesterol in phosphate-buffered saline solution containing disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium chloride, and water for injection.

After reconstitution, each 0.5-mL dose is formulated to contain 50 mcg of the recombinant gE antigen, 50 mcg of MPL, and 50 mcg of QS-21. Each dose also contains 20 mg of sucrose (as stabilizer), 4.385 mg of sodium chloride, 1 mg of DOPC, 0.54 mg of potassium dihydrogen phosphate, 0.25 mg of cholesterol, 0.160 mg of sodium dihydrogen phosphate dihydrate, 0.15 mg of disodium phosphate anhydrous, 0.116 mg of dipotassium phosphate, and 0.08 mg of polysorbate 80. After reconstitution, Shingrix® is a sterile, opalescent, and colorless to pale brownish liquid.

Shingrix® does not contain preservatives. Each dose may also contain residual amounts of host cell proteins (≤3.0%) and DNA (≤2.1 picograms) from the manufacturing process.

Efficacy of Shingrix® for the prevention of herpes zoster was 96.6% (95% confidence interval [CI] = 89.6-99.3) in persons ages 50-59 years and 97.4% (95% CI = 90.1-99.7) in persons ages 60-69 years. In study participants 70 years and older, vaccine efficacy was 91.3% (95% CI = 86.8-94.5). Vaccine efficacy in the first year after vaccination was 97.6% (95% CI = 90.9-99.8) and was 84.7% (95% CI = 69.0-93.4) or higher for the remaining 3 years of the study in persons 70 years of age and older. Efficacy for prevention of postherpetic neuralgia was 91.2% (95% CI = 75.9-97.7) in adults 50 years and older and 88.8% (95% CI = 68.7-97.1) in those 70 years and older.

RECOMMENDATIONS FOR USE OF RZV IN THE VFA PROGRAM

Eligible Persons

Adults 50 years of age and older may receive RZV provided by the VFA program if they are:

- Uninsured – no public or private health insurance coverage, OR
- Underinsured – health insurance does not cover RZV.

Note: If the patient's health insurance covers ZVL, but does not cover RZV, the patient is considered underinsured for the purpose of the VFA program.

ACIP Zoster Vaccine Recommendations

General use. RZV is recommended for the prevention of herpes zoster and related complications for immunocompetent adults 50 years of age and older, regardless of prior receipt of varicella vaccine or ZVL, and does not require screening for a history of chickenpox (varicella). RZV is preferred over ZVL for the prevention of herpes zoster and related complications.

Dosing schedule. RZV is administered in a two-dose schedule. Following the first dose of RZV, the second dose should be given 2–6 months later. The vaccine series need not be restarted if more than 6 months have elapsed since the first dose. If the second dose of RZV is given less than 4 weeks after the first, the second dose should be repeated. Two doses of the vaccine are necessary, regardless of prior history of herpes zoster or prior receipt of ZVL.

Make sure you have a plan in place to recall your patients for the second dose of the Shingrix® vaccine.

Timing of RZV for persons previously vaccinated with ZVL. Administer RZV if at least 2 months have elapsed since a patient 50 years and older received ZVL.

IMPORTANCE OF A STRONG MESSAGE FOR RZV

Providers should strongly recommend RZV along with other adult vaccines. Recommend RZV as the best way to protect against shingles and associated complications. Frame the conversation with your patients around the following messages:

- Shingles is common. There are about a million new cases each year in the United States.
- Anyone who has had chickenpox can get shingles. That means 95% of adults are at risk.
- One of three people in the United States will get shingles in their lifetime. The risk rises after age 50. Half of people living to age 85 have had or will get shingles.
- Among those who get shingles, more than one third will develop serious complications. The risk of complications rises after age 60.
- RZV is very effective in preventing shingles.

Herpes zoster vaccination rates remain low despite its benefits. In 2016, only 36% of California adults 60 years and older reported receiving ZVL, which has been in use since 2006. The proportion is significantly lower for the 60-64 years group, with only 20% of those reporting receipt of ZVL. Providers should use every opportunity to strongly recommend RZV and all other recommended adult vaccines.

For additional tips and resources, please visit: www.cdc.gov/vaccines/vpd/shingles/index.html.

ADMINISTRATION

Reconstitution

Shingrix® is to be reconstituted only with the accompanying adjuvant suspension. Prepare Shingrix® by reconstituting the lyophilized varicella zoster virus glycoprotein E (gE) antigen component with the accompanying $AS01_B$ adjuvant suspension component. The reconstituted vaccine should be an opalescent, colorless to pale brownish liquid. A single dose after reconstitution is 0.5 mL.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

1. Cleanse both vial stoppers.
2. Withdraw the entire contents of the vial containing the adjuvant suspension (blue-green cap) into a sterile syringe.
3. Add the entire contents of the syringe into the vial containing the lyophilized powder (brown cap).
4. Gently shake the vial to thoroughly mix contents until lyophilized powder is completely dissolved.

Administration

After reconstitution, withdraw 0.5 mL from the vial containing the reconstituted vaccine and administer intramuscularly. If the vaccine is inadvertently administered subcutaneously, it is not necessary to repeat vaccination.

Use a separate sterile needle and sterile syringe for each patient. The preferred site for intramuscular injection is the deltoid region of the upper arm.

Providers should consider observing patients (with patients seated or lying down) for 15 minutes after they are vaccinated.

Providers should report any vaccine administration error and associated contributing factors to the National Vaccine Errors Reporting Program (VERP) at http://verp.ismp.org/. Examples of potential errors include Shingrix® administered to a child who was supposed to be vaccinated with varicella vaccine. As a part of the report, providers can make recommendations for error prevention. This surveillance program aims to prevent future errors by identifying trends, creating targeted education efforts, and making changes to product labeling and design.

ADMINISTRATION WITH OTHER VACCINES

Shingrix® can be administered concomitantly with other adult vaccines. Do not mix this vaccine or any of its components with any other vaccine or diluent in the same syringe or vial. All vaccines should be given at separate anatomic sites with separate syringes.

Concomitant administration of Shingrix® with Fluarix Quadrivalent (influenza vaccine) (QIV) has been studied, and there was no evidence for interference in the immune response to either vaccine or safety concerns.

Shingrix® and pneumococcal vaccine may be administered at the same visit if the person is eligible for both. When both pneumococcal conjugate vaccine PCV13 and PPSV23 are recommended for an adult, PCV13 should always be administered first and may be administered concomitantly with Shingrix®.

Counseling for reactogenicity (See also next page: potential vaccine reactions)
Before vaccination, providers should counsel RZV recipients about expected systemic and local reactogenicity. Reactions to the first dose did not strongly predict reactions to the second dose. Vaccine recipients should be encouraged to complete the series even if they experienced a grade 1-3 reaction to the first dose of RZV.

PACKAGING

Shingrix® is supplied as two components as either one dose or 10-dose packages of single-dose vials of lyophilized gE antigen component (brown cap) and a single-dose vial of adjuvant suspension component (blue-green cap) (packaged without syringes or needles).

An outer package of one dose contains one vial each of Adjuvant Suspension Component and Lyophilized gE Antigen Component.

An outer package of 10 doses contains 10 vials each of Adjuvant Suspension Component and Lyophilized gE Antigen Component.

STORAGE – DO NOT FREEZE!

- Please keep all vials stored in the original carton.
- SHINGRIX® should **be refrigerated** between 2° and 8°C (36° and 46°F)
- Do not freeze. Protect from light.

Storage before Reconstitution

Store both the adjuvant and the antigen components refrigerated between 2° and 8°C (36° and 46°F). Protect vials from light. **Do not freeze**. **Do not use** vials of adjuvant or antigen that have been frozen.

Storage after Reconstitution

After reconstitution, administer Shingrix® immediately or store refrigerated between 2° and 8°C (36° and 46°F) and use within 6 hours. Discard reconstituted vaccine if not used within 6 hours. **Do not freeze**. **Do not use** vaccine that has been frozen, and complete a wastage form.

POTENTIAL VACCINE REACTIONS

Serious adverse events (an undesirable experience associated with the vaccine that results in death, hospitalization, disability, or requires medical or surgical intervention to prevent a serious outcome) were examined in eight studies, which included 29,965 subjects 50 years and older. Overall, rates of serious adverse events over the study periods were similar in the RZV and placebo groups.

Injection-site and systemic grade 3 solicited adverse events (reactions related to vaccination which were severe enough to prevent normal activities) were actively surveyed in eight studies involving 10,590 subjects. The incidence of solicited local and general symptoms was higher in subjects who received Shingrix® than in subjects who received control (placebo or other vaccines). Whereas there were no differences in the proportions of local grade 3 reactions between dose 1 and dose 2, systemic

grade 3 reactions were reported more frequently after dose 2. Overall, the most common adverse reactions (grades 1-3) were pain at injection site (78%), myalgia (45%), and fatigue (45%). The incidence of solicited local and general symptoms was lower in subjects aged 70 years and older compared with those aged 50 to 69 years. The majority of solicited local adverse reactions and general adverse events seen with Shingrix® had a median duration of 2 to 3 days.

Providers should report suspected reactions to Zoster vaccines or any other vaccine to the Vaccine Adverse Events Reporting System (VAERS) at 800-822-7967 (toll-free) or at http://vaers.hhs.gov.

CONTRAINDICATIONS

Shingrix® should not be administered to persons:

- With a known hypersensitivity to the active substance or to any component of the vaccine.
- Known to be seronegative for varicella. Screening for a history of varicella (verbally or via laboratory serology) before vaccination for herpes zoster is not recommended. However, in persons known to be VZV negative via serologic testing, ACIP guidelines for varicella vaccination should be followed. Shingrix® is not indicated for the prevention of chickenpox (varicella).
- Experiencing an acute episode of herpes zoster. Shingrix® is not a treatment for herpes zoster or postherpetic neuralgia (PHN). If a patient is experiencing an episode of herpes zoster, vaccination should be delayed until the acute stage of the illness is over and symptoms abate.

PRECAUTIONS

Adults with a minor acute illness, such as a cold, can receive Shingrix®. Adults with a moderate or severe acute illness should usually wait until they recover before getting the vaccine. This includes anyone with a temperature of 101.3°F or higher.

SPECIAL POPULATIONS

Pregnancy. Shingrix® has not been studied in pregnant women or women who are breastfeeding. Providers should consider delaying Shingrix® vaccination for these women.

Persons with a history of herpes zoster. Herpes zoster can recur. Adults with a history of herpes zoster should receive Shingrix®. If a patient is experiencing an episode of herpes zoster, vaccination should be delayed until the acute stage of the illness is over and symptoms abate.

Immunocompromised persons. Shingrix® is recommended for use in persons taking low-dose immunosuppressive therapy and persons anticipating immunosuppression or who have recovered from an immunocompromising illness.

ACIP has not made recommendations regarding the use of Shingrix® in immunocompromised persons and those on moderate to high doses of immunosuppressive therapy.

ZOSTER VACCINE SUPPLY

Shingrix®

Unprecedented high demand for Shingrix® vaccine earlier this year quickly surpassed GSK's projected supply levels. In order to manage available supply, GSK implemented order limits for privately

purchased doses in early May, and anticipates limits will continue to be in place for the remainder of 2018. In the interim, GSK continues to work towards increasing vaccine supply levels, while monitoring demand, and ensuring equitable supply distribution across both public and private segments throughout the second half of 2018.

Due to supply constraints, the number of doses available through CDC is also very limited. Each state has received a limited number of allocated doses. As a result, ordering limitations will be applied during the initial introduction of this vaccine among California VFA providers and local health departments.

Zostavax®

Effective July 1, 2018, CDC has discontinued this product for ordering, and it is no longer available for routine ordering through the California VFA Program.

Given limited supplies of Zoster vaccines, all VFA providers should ensure any remaining Zostavax® doses in inventory are depleted before placing any vaccine request for the new Shingles vaccine. Any unexpired doses on hand should not be returned to the program.

ORDERING

How to Order

Shingrix® is now available for limited ordering through the 317-vaccine order form. Due to supply constraints, ordering will be open ONLY for providers who have previously implemented routine use of Zostavax® vaccine among VFA-eligible adults served by the practice.

Order approval will be based on 1) the average number of Zoster vaccine doses administered per month during 2018; 2) estimated 2-month need based on administration data; 3) available on-hand inventories of Zostavax®; 4) available vaccine supply on California's allocation.

Ordering will be limited for providers with sufficient inventory of Zostavax® on hand. Continue to use your existing Zostavax® supply as we deal with the temporary shortage of Shingrix® vaccine. Do not miss an opportunity to vaccinate VFA-eligible patients.

DOCUMENTATION - HYPERLINKS

1) ACIP recommendations: MMWR, January 26, 2018; 67(3); 103–108
   https://www.cdc.gov/mmwr/volumes/67/wr/mm6703a5.htm
2) Product Insert, RZV Shingrix®
   https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM581605.pdf
3) Vaccine Information State (VIS) for RZV
   http://www.immunize.org/vis/zoster-recombinant.pdf
4) Vaccine Injury Compensation Program (VICP): Zoster vaccines are **not** covered by VICP.
5) RZV Information for Healthcare Professionals – CDC
   https://www.cdc.gov/vaccines/vpd/shingles/hcp/shingrix/index.html