

PRODUCT CIRCULAR

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ZOSTAVAX®
Zoster Vaccine Live (Oka/Merck)
Refrigerator stable

THERAPEUTIC CLASS

ZOSTAVAX is a lyophilized preparation of the Oka/Merck strain of live, attenuated varicella-zoster virus (VZV).

COMPOSITION

ZOSTAVAX, when reconstituted as directed, is a sterile preparation for subcutaneous administration. Each 0.65-mL dose contains a minimum of 19,400 PFU (plaque-forming units) of Oka/Merck VZV when reconstituted and stored at room temperature for up to 30 minutes.

INDICATIONS

ZOSTAVAX is indicated for:

- prevention of herpes zoster (shingles)
- prevention of postherpetic neuralgia (PHN) in individuals who develop herpes zoster despite vaccination with ZOSTAVAX.
- reduction of acute and chronic zoster-associated pain in individuals who develop herpes zoster despite vaccination with ZOSTAVAX.

ZOSTAVAX is not indicated for the treatment of zoster or postherpetic neuralgia (PHN) or zoster-associated pain.

ZOSTAVAX is indicated for immunization of individuals 50 years of age or older.

ZOSTAVAX can be administered concomitantly with inactivated influenza vaccine (see **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION.

Do not inject intravascularly.

Individuals should receive a single dose. At present, the duration of protection after vaccination with ZOSTAVAX is unknown. In the Shingles Prevention Study (SPS), protection was demonstrated through 4 years of follow-up. The need for revaccination has not yet been defined.

ZOSTAVAX is not a treatment for zoster or PHN.

ZOSTAVAX can be administered concomitantly with inactivated influenza vaccine using separate syringes.

Reconstitute immediately upon removal from the refrigerator.

To reconstitute the vaccine, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine virus.

Vial of diluent :

To reconstitute the vaccine, first withdraw the entire contents of the diluent vial into a syringe. Inject all of the diluent in the syringe into the vial of lyophilized vaccine and gently agitate to mix thoroughly. Withdraw the entire contents into a syringe and inject the total volume of reconstituted vaccine subcutaneously, preferably into the upper arm (preferably in the deltoid region).

IT IS RECOMMENDED THAT THE VACCINE BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION, TO MINIMIZE LOSS OF POTENCY. DISCARD RECONSTITUTED VACCINE IF IT IS NOT USED WITHIN 30 MINUTES.

Do not freeze reconstituted vaccine.

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of ZOSTAVAX because these substances may inactivate the vaccine virus.

A separate sterile needle and syringe should be used for administration of ZOSTAVAX to prevent transfer of infectious diseases.

Needles should be disposed of properly and should not be recapped.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. ZOSTAVAX when reconstituted is a semi-hazy to translucent, off white to pale yellow liquid.

CONTRAINDICATIONS

History of hypersensitivity to any component of the vaccine, including gelatin.

History of anaphylactic/anaphylactoid reaction to neomycin (each dose of reconstituted vaccine contains trace quantities of neomycin). Neomycin allergy generally manifests as a contact dermatitis. However, a history of contact dermatitis due to neomycin is not a contraindication to receiving live virus vaccines.

ZOSTAVAX is a live, attenuated varicella-zoster vaccine and administration to individuals who are immunosuppressed or immunodeficient may result in disseminated varicella-zoster virus disease, including fatal outcomes .

Primary and acquired immunodeficiency states due to conditions such as: acute and chronic leukemias; lymphoma; other conditions affecting the bone marrow or lymphatic system; immunosuppression due to HIV/AIDS (see **SPECIAL POPULATION** and **SIDE EFFECTS**); cellular immune deficiencies.

Immunosuppressive therapy (including high-dose corticosteroids) (see **SIDE EFFECTS**); however, ZOSTAVAX is not contraindicated for use in individuals who are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids or in patients who are receiving corticosteroids as replacement therapy, e.g., for adrenal insufficiency.

Active untreated tuberculosis.

Pregnancy (see **PREGNANCY**).

PRECAUTIONS

The health care provider should question the patient about reactions to a previous dose of any VZV-containing vaccines (see **CONTRAINDICATIONS**).

As with any vaccine, adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactic/anaphylactoid reaction occur.

Deferral of vaccination should be considered in the presence of fever $>38.5^{\circ}\text{C}$ ($>101.3^{\circ}\text{F}$).

The safety and efficacy of ZOSTAVAX have not been established in adults who are known to be infected with human immunodeficiency virus (HIV) with or without evidence of immunosuppression. A phase II safety and immunogenicity study in HIV-infected adults with conserved immune function has been completed (see **SPECIAL POPULATION** and **SIDE EFFECTS**).

As with any vaccine, vaccination with ZOSTAVAX may not result in protection of all vaccine recipients.

Transmission

In clinical trials with ZOSTAVAX, transmission of the vaccine virus has not been reported. However, post-marketing experience with varicella vaccines suggests that transmission of vaccine virus may occur rarely between vaccinees who develop a varicella-like rash and susceptible contacts. Transmission of vaccine virus from varicella vaccine recipients who do not develop a varicella-like rash has also been reported. This is a theoretical risk for vaccination with ZOSTAVAX. The risk of transmitting the attenuated vaccine virus to a susceptible individual should be weighed against the risk of developing natural zoster that could be transmitted to a susceptible individual.

PREGNANCY

Animal reproduction studies have not been conducted with ZOSTAVAX. It is also not known whether ZOSTAVAX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, naturally-occurring VZV infection is known to sometimes cause fetal harm. Therefore, ZOSTAVAX should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination (see **CONTRAINDICATIONS**).

NURSING MOTHERS

It is not known whether VZV is secreted in human milk. Therefore, because some viruses are secreted in human milk, caution should be exercised if ZOSTAVAX is administered to a nursing woman.

PEDIATRIC USE

ZOSTAVAX is not recommended for use in this age group.

GERIATRIC USE

The mean age of subjects enrolled in the largest (N=38,546) clinical study of ZOSTAVAX was 69 years (range 59-99 years). Of the 19,270 subjects who received ZOSTAVAX, 10,378 were 60-69 years of age, 7,629 were 70-79 years of age, and 1,263 were 80 years of age or older. ZOSTAVAX was demonstrated to be generally safe and effective in this population.

DRUG INTERACTIONS

ZOSTAVAX must not be mixed with any other medicinal product in the same syringe. Other medicinal products must be given as separate injections and at different body sites.

Concurrent administration of ZOSTAVAX and antiviral medications known to be effective against VZV has not been evaluated.

ZOSTAVAX and PNEUMOVAX 23 should not be given concomitantly because concomitant use resulted in reduced immunogenicity of ZOSTAVAX. Consider administration of the two vaccines separated by at least 4 weeks.

SIDE EFFECTS

In clinical trials, ZOSTAVAX has been evaluated for general safety in more than 32,000 adults 50 years of age or older. ZOSTAVAX was generally well tolerated.

ZOSTAVAX Efficacy and Safety Trial (ZEST) in Subjects 50 to 59 Years of Age

In the ZEST study, subjects received a single dose of either ZOSTAVAX (n=11,184) or placebo (n=11,212) and were monitored for safety throughout the study. During the study, a vaccine-related serious adverse experience was reported for 1 subject vaccinated with ZOSTAVAX (anaphylactic reaction).

All subjects received a vaccination report card (VRC) to record adverse events occurring from Days 1 to 42 postvaccination in addition to undergoing routine safety monitoring throughout the study.

The following very common ($\geq 1/10$) and common ($\geq 1/100$, $< 1/10$) vaccine-related injection-site and systemic adverse experiences were reported in the ZEST study. Several adverse experiences were solicited (Days 1-5 postvaccination) and are designated with the * symbol.

Nervous system disorder

Common: headache

General disorders and administration site conditions

Very common: erythema, * pain, * swelling, * pruritus

Common: hematoma, warmth, induration

Musculoskeletal and connective tissue disorders

Common: pain in extremity

The overall incidence of vaccine-related injection-site adverse experiences was significantly greater for subjects vaccinated with ZOSTAVAX versus subjects who received placebo (63.9% for ZOSTAVAX and 14.4% for placebo).

Within the 42-day post vaccination reporting period in the ZEST, noninjection-site zosteriform rashes were reported by 34 subjects (19 for ZOSTAVAX and 15 for placebo). Of 24 specimens that were adequate for Polymerase Chain Reaction (PCR) testing, wild-type VZV was detected in 10 (3 for ZOSTAVAX, 7 for

placebo) of these specimens. The Oka/Merck strain of VZV was not detected from any of these specimens.

Within the same 42-day postvaccination reporting period in the ZEST, varicella-like rashes were reported by 124 subjects (69 for ZOSTAVAX and 55 for placebo). Of 23 specimens that were available and adequate for PCR testing, VZV was detected in one of these specimens from the group of subjects who received ZOSTAVAX; however, the virus strain (wild type or Oka/Merck strain) could not be determined.

Shingles Prevention Study (SPS) in Subjects 60 Years of Age and Older

In the largest of these trials, the Shingles Prevention Study (SPS), 38,546 subjects received a single dose of either ZOSTAVAX (n=19,270) or placebo (n=19,276) and were monitored for safety throughout the study. During the study, vaccine-related serious adverse experiences were reported for 2 subjects vaccinated with ZOSTAVAX (asthma exacerbation and polymyalgia rheumatica) and 3 subjects who received placebo (Goodpasture's syndrome, anaphylactic reaction, and polymyalgia rheumatica).

In the Adverse Event Monitoring Substudy, a subgroup of individuals from the SPS (n=3,345 received ZOSTAVAX and n=3,271 received placebo) were provided vaccination report cards to record adverse events occurring from Days 0 to 42 postvaccination in addition to undergoing routine safety monitoring throughout the study.

The following very common ($\geq 1/10$) and common ($\geq 1/100$, $< 1/10$) vaccine-related injection-site and systemic adverse experiences were reported in the Adverse Event Monitoring Substudy. Most of these adverse experiences were reported as mild in intensity. Several adverse experiences were solicited (Days 0-4 postvaccination) and are designated with the * symbol.

Nervous system disorder

Common: headache

General disorders and administration site conditions

Very common: erythema, * pain/tenderness, * swelling*

Common: hematoma, pruritus, warmth

The overall incidence of vaccine-related injection-site adverse experiences was significantly greater for subjects vaccinated with ZOSTAVAX versus subjects who received placebo (48% for ZOSTAVAX and 17% for placebo).

The remainder of subjects in the SPS received routine safety monitoring, but were not provided report cards. The types of events reported in these patients were generally similar to the subgroup of patients in the Adverse Event Monitoring Substudy.

Within the 42-day postvaccination reporting period in the SPS, the number of reported zosteriform rashes among all subjects was small (17 for ZOSTAVAX, 36 for placebo; $p=0.009$). Of these 53 zosteriform rashes, 41 had specimens that were available and adequate for PCR testing. Wild-type VZV was detected in 25 (5 for ZOSTAVAX, 20 for placebo) of these specimens. The Oka/Merck strain of VZV was not detected from any of these specimens.

Within the same 42-day postvaccination reporting period in the SPS, the number ($n=59$) of reported varicella-like rashes was also small. Of these varicella-like rashes, 10 had specimens that were available and adequate for PCR testing. VZV was not detected in any of these specimens.

Other Studies

In other clinical trials in support of the initial licensure of the frozen formulation of ZOSTAVAX, the reported rates of noninjection-site zosteriform and varicella-like rashes within 42 days postvaccination were also low in both zoster vaccine recipients and placebo recipients. Of 17 reported varicella-like rashes and non-injection site zoster-like rashes, 10 specimens were available and adequate for PCR testing, and 2 subjects had varicella (onset Day 8 and 17) confirmed to be Oka/Merck strain.

In clinical trials evaluating ZOSTAVAX in subjects 50 years of age or older, including a study of concomitantly administered inactivated influenza vaccine, the safety profile was generally similar to that seen in the Adverse Event Monitoring Substudy of the SPS. However, in these trials, a higher rate of injection-site adverse experiences of mild-to-moderate intensity was reported among subjects 50-59 years of age compared with subjects ≥ 60 years of age.

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX was administered to 100 subjects 50 years of age or older with a history of herpes zoster (HZ) prior to vaccination to assess immunogenicity of ZOSTAVAX and the safety profile. In this clinical trial, the safety profile was generally similar to that seen in the Adverse Event Monitoring Substudy of the SPS.

To address concerns for individuals with an unknown history of vaccination with ZOSTAVAX, the safety and tolerability of a second dose of ZOSTAVAX was evaluated. In a placebo-controlled, double-blind study, 98 adults 60 years of age or older received a second dose of ZOSTAVAX 42 days following the initial dose; the vaccine was generally well tolerated. The frequency of vaccine-related adverse experiences after the second dose of ZOSTAVAX was generally similar to that seen with the first dose.

Immunogenicity in subjects with HIV infection

In a double-blind, placebo-controlled randomized clinical trial, ZOSTAVAX was administered as a two-dose regimen to human immunodeficiency virus (HIV)-infected adults (18 years of age or older) on potent combination antiretroviral therapy with conserved immune function (CD4+ T cell count \geq 200 cells/ μ L). Although a two-dose regimen was used in this study, ZOSTAVAX is administered as a single dose regimen (See **DOSAGE & ADMINISTRATION**). In this clinical trial, a total of 295 subjects received dose 1 and 286 subjects received dose 2. All vaccinated study patients were followed for adverse experiences. Vaccine relatedness was determined by the investigator based upon blinded data. To evaluate the adverse experiences temporally associated with study vaccination, patients were given a Vaccination Report Card (VRC) to record any injection-site adverse experiences, systemic adverse experiences, elevated temperatures, and rashes through Week 6 following each vaccination. Patients were followed for serious adverse experiences, regardless of whether the event was related to the study vaccine, throughout the course of the study (through Week 24 following dose 1). In this clinical trial, the safety profile was generally similar to that seen in the Adverse Event Monitoring Substudy of the SPS. (See **CONTRAINDICATIONS** regarding immunosuppression due to HIV/AIDS.)

Post-marketing Experience

The following additional adverse reactions have been identified during post-marketing use of ZOSTAVAX. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Gastrointestinal disorders: nausea

Infections and infestations: herpes zoster (vaccine strain)

Skin and subcutaneous tissue disorders: rash

Musculoskeletal and connective tissue disorders: arthralgia; myalgia

General disorders and administration site conditions: injection-site rash; injection-site urticaria; pyrexia; transient injection-site lymphadenopathy

Immune system disorders: hypersensitivity reactions including anaphylactic reactions

Eye Disorders: Necrotizing retinitis (patients on immunosuppressive therapy)

Nervous system disorders: Guillain-Barré syndrome; facial paralysis

SPECIAL POPULATION

Immunogenicity in subjects with HIV infection

In a double-blind, placebo-controlled randomized clinical trial, ZOSTAVAX was administered as a two-dose regimen to human immunodeficiency virus (HIV)-infected adults (18 years of age or older) on potent combination antiretroviral therapy with conserved immune function (CD4+ T cell count \geq 200 cells/ μ L). Although a two-dose regimen was used in this study, ZOSTAVAX is administered as a single dose regimen (see **DOSAGE & ADMINISTRATION**). In this study, a total of 295 subjects received dose 1 and 286 subjects received dose 2. Compared with placebo, ZOSTAVAX induced a higher VZV-specific

gpELISA antibody GMT at Week 6 (6 weeks following dose 1) and Week 12 (6 weeks following dose 2) (GMT of 534.4 and 530.3 vs. 263.7 and 250.3 gpELISA units/ml, respectively). The geometric mean fold-rises of the VZV antibody response, as measured by gpELISA, from baseline to Week 6 and Week 12 were 1.78 (95% CI: [1.64 to 1.92]) and 1.80 (95% CI: [1.66 to 1.95]), respectively, in vaccine recipients and 1.05 (95% CI: [0.98 to 1.12]) and 1.04 (95% CI: [0.96 to 1.13]), respectively, in placebo recipients. (See **CONTRAINDICATIONS** regarding immunosuppression due to HIV/AIDS.)

OVERDOSAGE

There are no data with regard to overdose.

STORAGE

Storage

During shipment, to ensure that there is no loss of potency, the vaccine must be maintained at a temperature of 8°C (46°F) or colder, but not to exceed temperature lower than -50°C (-58°F). Use of dry ice may subject ZOSTAVAX to temperatures colder than -50°C (-58°F).

ZOSTAVAX **SHOULD BE STORED REFRIGERATED** at a temperature of 2 to 8°C (36 to 46°F) or colder until it is reconstituted for injection (see **DOSAGE AND ADMINISTRATION**). The diluent should be stored separately at room temperature (20 to 25°C, 68 to 77°F) or in the refrigerator (2 to 8°C, 36 to 46°F).

Before reconstitution, protect from light.

DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.

DO NOT FREEZE THE RECONSTITUTED VACCINE.

AVAILABILITY

ZOSTAVAX is supplied as a single dose vial of lyophilized vaccine and a vial (0.7 mL) of diluent.

Imported by **MSD (THAILAND) LTD.**
Bangkok, Thailand