

## PRODUCT MONOGRAPH

### ZOSTAVAX<sup>®</sup> II

(zoster vaccine live, attenuated [Oka/Merck], refrigerator-stable)

Powder for suspension for injection

Live, attenuated virus varicella-zoster vaccine

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## ZOSTAVAX® II

(zoster vaccine live, attenuated [Oka/Merck], refrigerator-stable)

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Subcutaneous injection	Lyophilized powder reconstituted for injection  Immunogen: varicella-zoster virus ≥ 19,400 PFU (plaque-forming units)	Hydrolyzed porcine gelatin and neomycin  <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

#### DESCRIPTION

ZOSTAVAX® II (zoster vaccine live, attenuated [Oka/Merck], refrigerator-stable) is a live, attenuated virus vaccine (a lyophilized preparation of the Oka/Merck strain of varicella-zoster virus<sup>\*</sup>).

#### INDICATIONS AND CLINICAL USE

ZOSTAVAX® II is indicated for the prevention of herpes zoster (shingles).

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

#### 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.

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\* Produced on human diploid cells (MRC-5)

ZOSTAVAX<sup>®</sup> II 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 WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS and CLINICAL TRIALS, Immunogenicity in subjects with HIV infection); cellular immune deficiencies.

Immunosuppressive therapy (including high-dose corticosteroids) (see ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions); however, ZOSTAVAX<sup>®</sup> II 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 WARNINGS AND PRECAUTIONS - Pregnant Women).

## **WARNINGS AND PRECAUTIONS**

### **General**

The health care provider should question the patient about reactions to a previous dose of any varicella-zoster virus (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°C (> 101.3°F).

ZOSTAVAX<sup>®</sup> II does not protect all individuals against the development of herpes zoster or its sequelae (see ACTION AND CLINICAL PHARMACOLOGY and CLINICAL TRIALS).

The duration of protection beyond 4 years after vaccination with ZOSTAVAX<sup>®</sup>, the frozen formulation of zoster vaccine live, attenuated [Oka/Merck] is unknown. The need for revaccination has not been defined.

ZOSTAVAX<sup>®</sup> II has not been studied in individuals who have previously experienced an episode of herpes zoster.

### **Transmission**

In clinical trials with ZOSTAVAX<sup>®</sup> or ZOSTAVAX<sup>®</sup> II, 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 and is therefore a theoretical risk for vaccination with ZOSTAVAX<sup>®</sup> or ZOSTAVAX<sup>®</sup> II. The risk of transmitting the attenuated vaccine virus to a susceptible individual should be weighed against the risk of developing natural herpes zoster and potentially transmitting wild-type VZV to a susceptible contact.

### **Special Populations**

**Geriatric:** The mean age of subjects enrolled in the largest (N=38,546) clinical study of ZOSTAVAX<sup>®</sup> was 69 years (range 59-99 years). Of the 19,270 subjects who received ZOSTAVAX<sup>®</sup>, 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<sup>®</sup> was demonstrated to be generally safe and effective in this population.

**Pregnant Women:** There are no studies in pregnant women. It is also not known whether ZOSTAVAX<sup>®</sup> II can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. However naturally-occurring varicella-zoster virus infection is known to sometimes cause foetal harm. Therefore, ZOSTAVAX<sup>®</sup> II should not be administered to pregnant women; furthermore, pregnancy should be avoided for three months following vaccination (see CONTRAINDICATIONS).

**Nursing Women:** 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<sup>®</sup> II is administered to a nursing woman.

**Pediatrics:** ZOSTAVAX<sup>®</sup> II is not recommended for use in this age group.

**HIV-AIDS Patients:** The safety and efficacy of ZOSTAVAX<sup>®</sup> II have not been established in adults who are known to be infected with 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 ADVERSE REACTIONS and CLINICAL TRIALS).

**Immunocompromised Subjects:** Data are not available regarding the use of ZOSTAVAX<sup>®</sup> II in immunocompromised subjects (see CONTRAINDICATIONS).

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

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

### **Clinical Trial Adverse Drug Reactions**

### ZOSTAVAX<sup>®</sup> 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<sup>®</sup> (n=11,184) or placebo (n=11,212) and were monitored for general safety throughout the study. During the study, a vaccine-related serious adverse experience was reported for 1 subject vaccinated with ZOSTAVAX<sup>®</sup> (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.

Vaccine-related injection-site and systemic adverse experiences reported at an incidence of  $\geq 1\%$  are shown in Table 1. The overall incidence of vaccine-related injection-site adverse experiences was significantly greater for subjects vaccinated with ZOSTAVAX<sup>®</sup> versus subjects who received placebo (63.9% for ZOSTAVAX<sup>®</sup> and 14.4% for placebo).

**Table 1**  
**Vaccine-Related Injection-Site and Systemic Adverse Experiences Reported in  $\geq 1\%$  of Adults Who Received ZOSTAVAX<sup>®</sup> or Placebo (1-42 Days Postvaccination) in the ZOSTAVAX<sup>®</sup> Efficacy and Safety Trial**

<b>Adverse Experience</b>	<b>ZOSTAVAX<sup>®</sup></b> (N = 11,094) %	<b>Placebo</b> (N = 11,116) %
<i>Injection-Site</i>		
Pain <sup>†</sup>	53.9	9.0
Erythema <sup>†</sup>	48.1	4.3
Swelling <sup>†</sup>	40.4	2.8
Pruritus	11.3	0.7
Warmth	3.7	0.2
Hematoma	1.6	1.6
Induration	1.1	0.0
<i>Systemic</i>		
Headache	9.4	8.2
Pain in extremity	1.3	0.8

<sup>†</sup> Designates a solicited adverse experience. Injection-site adverse experiences were solicited only from Days 1-5 postvaccination.

Within the 42-day postvaccination period in the ZEST, noninjection-site zoster-like rashes were reported by 34 subjects (19 for ZOSTAVAX<sup>®</sup> 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<sup>®</sup>, 7 for placebo) of these specimens. The Oka/Merck strain of VZV was not detected from any of these specimens.

Of reported varicella-like rashes (n=124, 69 for ZOSTAVAX<sup>®</sup> and 55 for placebo), 23 had 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<sup>®</sup>; 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<sup>®</sup> (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<sup>®</sup> (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<sup>®</sup> 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.

**Table 2**  
**Number of Subjects with ≥ 1 Serious Adverse Events (0-42 Days Postvaccination) in the Shingles Prevention Study**

<b>Cohort</b>	<b>ZOSTAVAX<sup>®</sup></b> n/N %	<b>Placebo</b> n/N %	<b>Relative Risk</b> <b>(95% CI)</b>
<b>Overall Study Cohort</b>			
All ages	255/18671 1.4%	254/18717 1.4%	1.01 (0.85, 1.20)
60-69 years old	113/10100 1.1%	101/10095 1.0%	1.12 (0.86, 1.46)
≥ 70 years old	142/8571 1.7%	153/8622 1.8%	0.93 (0.74, 1.17)
<b>AE Monitoring Substudy Cohort</b>			
All ages	64/3326 1.9%	41/3249 1.3%	1.53 (1.04, 2.25)
60-69 years old	22/1726 1.3%	18/1709 1.1%	1.21 (0.66, 2.23)
≥ 70 years old	42/1600 2.6%	23/1540 1.5%	1.76 (1.07, 2.89)

N = number of subjects in cohort with safety follow-up  
n = number of subjects reporting an SAE 0-42 Days postvaccination

The incidence of death was similar in the groups receiving ZOSTAVAX<sup>®</sup> or placebo during the Days 0-42 postvaccination period: 14 deaths occurred in the group of subjects who received ZOSTAVAX<sup>®</sup> and 16 deaths occurred in the group of subjects who received placebo. The most common reported cause of death was cardiovascular disease (10 in the group of subjects who received ZOSTAVAX<sup>®</sup>, 8 in the group of subjects who received placebo). The overall incidence of death occurring at any time during the study was similar between vaccination groups: 793 deaths (4.1%) occurred in subjects who received ZOSTAVAX<sup>®</sup> and 795 deaths (4.1%) in subjects who received placebo.

Vaccine-related injection-site and systemic adverse experiences reported at an incidence  $\geq 1\%$  are shown in Table 3. Most of these adverse experiences were reported as mild in intensity.

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

**Table 3**  
**Vaccine-Related Injection-Site and Systemic Adverse Experiences Reported in  $\geq 1\%$  of Adults Who Received ZOSTAVAX<sup>®</sup> or Placebo (0-42 Days Postvaccination) in the Adverse Event Monitoring Substudy of the Shingles Prevention Study**

<b>Adverse Experience</b>	<b>ZOSTAVAX<sup>®</sup></b> (N = 3345) %	<b>Placebo</b> (N = 3271) %
<i>Injection-Site</i>		
Erythema <sup>†</sup>	35.6	6.9
Pain/tenderness <sup>†</sup>	34.3	8.6
Swelling <sup>†</sup>	26.1	4.5
Hematoma	1.6	1.4
Pruritus	7.1	1.0
Warmth	1.7	0.3
<i>Systemic</i>		
Headache	1.4	0.9

<sup>†</sup> Designates a solicited adverse experience. Injection-site adverse experiences were solicited only from Days 0-4 postvaccination.

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 noninjection-site zoster-like rashes among all subjects was small (17 for ZOSTAVAX<sup>®</sup>, 36 for placebo;  $p=0.009$ ). Of these 53 zoster-like rashes, 41 had specimens that were available and adequate for PCR testing. Wild-type VZV was detected in 25 (5 for ZOSTAVAX<sup>®</sup>, 20 for placebo) of these specimens. The Oka/Merck strain of VZV was not detected from any of these specimens.

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. The results of virus testing in subjects with varicella-like and zoster-like rashes should be interpreted with caution due to the number of samples that were not available for testing.

The numbers of subjects with elevated temperature ( $\geq 38.3^{\circ}\text{C}$  [ $\geq 101.0^{\circ}\text{F}$ ]) within 7 days post-vaccination were similar in the ZOSTAVAX<sup>®</sup> and the placebo vaccination groups [6 (0.2%) vs. 8 (0.3%), respectively].

## Other studies

In other clinical trials conducted prior to the completion of the SPS, the reported rates of noninjection-site zoster-like 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.

To address concerns for individuals with an unknown history of vaccination with ZOSTAVAX<sup>®</sup>, the safety and tolerability of a second dose of ZOSTAVAX<sup>®</sup> was evaluated. In a placebo-controlled, double-blind study, 98 adults 60 years of age or older received a second dose of ZOSTAVAX<sup>®</sup> 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<sup>®</sup> was generally similar to that seen with the first dose.

### Safety in subjects on chronic/maintenance systemic corticosteroids

Descriptive study P017 is an estimation study with no hypothesis testing. In this double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX<sup>®</sup> was administered to 206 subjects 60 years of age or older who were receiving chronic/maintenance systemic corticosteroid therapy at a daily dose equivalent of 5 to 20 mg of prednisone for at least 2 weeks prior to enrollment, and 6 weeks or more following vaccination to assess the immunogenicity and safety profile of ZOSTAVAX<sup>®</sup>. 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 from Days 1 to 42 postvaccination. 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 Day 182 postvaccination). 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 corticosteroids).

In another clinical study (P010), the safety and tolerability of the frozen formulation was compared to the refrigerator stable formulation. Subjects were randomized in a 1:1 ratio to receive either ZOSTAVAX<sup>®</sup> frozen (N=185) or ZOSTAVAX<sup>®</sup> II refrigerator-stable (N=183). No vaccine-related serious adverse experiences were reported, indicating that the study's primary safety hypothesis was met. In addition, there was a lower frequency of injection-site adverse experiences and a similar frequency of systemic adverse experiences reported after vaccination with the refrigerator-stable formulation than that seen with the frozen formulation.

Vaccine-related injection-site and systemic adverse experiences reported at an incidence  $\geq 1\%$  are shown in Table 4.

**Table 4**  
**Vaccine-Related Injection-site and Systemic Adverse Experience Reported in  $\geq 1\%$  of Adults Who Received ZOSTAVAX<sup>®</sup> II or ZOSTAVAX<sup>®</sup> (1-42 Days Post-Vaccination) in Study P010**

<b>Adverse Experience</b>	<b>ZOSTAVAX<sup>®</sup> II</b> (refrigerator-stable formulation) N= 180 %	<b>ZOSTAVAX<sup>®</sup></b> (frozen formulation) N= 183 %
<i>Injection-site</i>		
Erythema†	28.9	35.5
Pain†	26.7	38.3
Pruritus	7.2	8.2
Rash	0.6	1.1
Swelling†	24.4	32.8
Warmth	1.7	1.1
<i>Systemic</i>		
Myalgia	1.1	0.5
Dizziness	0.0	1.1
Headache	1.7	0.5
Pruritus	0.0	1.1

† Designates a solicited adverse experience. Injection-site adverse experiences were solicited only from Days 1-5 postvaccination.

### Safety in subjects with HIV infection

In a double-blind, placebo-controlled randomized clinical trial, ZOSTAVAX<sup>®</sup> 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/ $\mu$ L). Although a two-dose regimen was used in this study, ZOSTAVAX<sup>®</sup> is administered as a single dose regimen (see DOSAGE AND 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 Adverse Drug Reactions

The following additional adverse reactions have been identified during post-marketing use of ZOSTAVAX<sup>®</sup>. 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; injection-site lymphadenopathy.

**Immune system disorders:** hypersensitivity reactions including anaphylactic reactions.

**Eye Disorders:** Necrotizing retinitis (patients on immunosuppressive therapy).

## **DRUG INTERACTIONS**

### **Overview**

ZOSTAVAX<sup>®</sup> II 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<sup>®</sup> II and antiviral medications known to be effective against VZV has not been evaluated.

### **Use with Other Vaccines**

ZOSTAVAX<sup>®</sup> II and PNEUMOVAX<sup>®</sup> 23 (pneumococcal vaccine, polyvalent, MSD Std.) should not be given concomitantly because concomitant use resulted in reduced immunogenicity of ZOSTAVAX<sup>®</sup> II (see CLINICAL TRIALS). Consider administration of the two vaccines separated by at least 4 weeks.

## **DOSAGE AND ADMINISTRATION**

### **Recommended Dose and Dosage Adjustment**

FOR SUBCUTANEOUS ADMINISTRATION.

Do not inject intravascularly.

Individuals should receive a single dose consisting of the entire content of the vial (approximately 0.65 mL).

ZOSTAVAX<sup>®</sup> II is not a treatment for zoster or postherpetic neuralgia (PHN). If an individual develops herpes zoster despite vaccination, active current standard of care treatment for herpes zoster should be considered.

At present, the duration of protection after vaccination with ZOSTAVAX<sup>®</sup> II 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.

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.

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 using a new needle, inject the total volume of reconstituted vaccine subcutaneously, preferably into the upper arm - 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<sup>®</sup> II because these substances may inactivate the vaccine virus.

It is important to use a separate sterile needle and syringe for each patient to prevent transfer of infectious agents from one individual to another.

Needles should be disposed of properly.

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

## **OVERDOSAGE**

There are no data with regard to overdose.

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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## **ACTION AND CLINICAL PHARMACOLOGY**

### **Herpes Zoster**

Herpes zoster (HZ), known also as shingles or simply “zoster”, is a manifestation of reactivation of VZV, which, as a primary infection, produces chickenpox (varicella).

Zoster is usually characterized by a unilateral, painful, vesicular cutaneous eruption with a dermatomal distribution. Although the blistering rash is the most distinctive feature of zoster, the most frequently debilitating symptom is pain, which may occur during the prodrome, the acute eruptive phase, and the postherpetic phase of the infection. During the acute eruptive phase, local pain has been reported to occur in up to 90% of immunocompetent individuals.

Anyone who has been infected with VZV, including those without a clinical history of varicella, is at risk for developing zoster, which is considered to be due to waning immunity to VZV. Nearly all adults are at risk for zoster.

The incidence and severity of zoster, as well as the frequency and severity of its complications, increase markedly with age, with two-thirds of the cases occurring in individuals older than 50 years of age. In recent studies, the lifetime risk of zoster has been estimated to be as high as 30% in the general population.

Zoster-associated hospitalization rates vary across countries and are estimated to range from 5 to 10 per 100,000 population for an average length of stay of 10 to 13 days. The proportion of zoster patients hospitalized increases with age, up to more than 10% in individuals over 65 years of age. Seventy to 80% of hospitalizations for zoster occur among immunocompetent individuals.

Zoster may be associated with serious complications such as PHN, scarring, bacterial superinfection, motor neuron palsies, pneumonia, encephalitis, Ramsay Hunt syndrome, visual impairment, hearing loss, and death.

### **Postherpetic Neuralgia**

Postherpetic neuralgia (PHN) constitutes the most common serious complication and cause of zoster-associated morbidity in the immunocompetent host. In the SPS, where a highly specific definition of PHN was used, PHN complicated 12.5% of zoster cases in the placebo group.

PHN has been described as tender, burning, throbbing, stabbing, shooting and/or sharp pain that can persist for months or even years and can also lead to emotional distress. Allodynia (pain from an innocuous stimulus) is present in at least 90% of patients with PHN and is typically described as the most distressing and debilitating type of pain. Several definitions of PHN are widely used in the medical community, including pain persisting longer than 90 days after the onset of the rash.

## **Evaluation of Clinical Efficacy Afforded by ZOSTAVAX<sup>®</sup>**

### ZOSTAVAX<sup>®</sup> Efficacy and Safety Trial (ZEST) in Subjects 50 to 59 Years of Age

In the ZOSTAVAX<sup>®</sup> Efficacy and Safety Trial (ZEST), a placebo-controlled, double-blind clinical trial, 22,439 subjects 50 to 59 years of age were randomized to receive a single dose of either ZOSTAVAX<sup>®</sup> (n=11,211) or placebo (n=11,228) and were followed for the development of zoster for a median of 1.3 years (range 0 to 2 years). All suspected zoster cases were adjudicated by a clinical evaluation committee. Final determination of zoster cases was made by Polymerase Chain Reaction (PCR) [86%], or in the absence of virus detection, as determined by a clinical evaluation committee [14%].

ZOSTAVAX<sup>®</sup> significantly decreased the incidence of zoster compared with placebo (30 cases [2.0/1000 person-years] vs. 99 cases [6.6/1000 person-years], respectively; p<0.001). The protective efficacy of ZOSTAVAX<sup>®</sup> against zoster was 69.8% (95% CI: [54.1 to 80.6%]).

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

In the Shingles Prevention Study (SPS), a placebo-controlled, double-blind clinical trial of ZOSTAVAX<sup>®</sup> frozen formulation, 38,546 subjects 60 years of age or older were randomized to receive a single dose of either ZOSTAVAX<sup>®</sup> (n=19,270) or placebo (n=19,276) and were followed for the development of zoster for a median of 3.1 years (range 31 days to 4.9 years). The study excluded people who were immunocompromised, anyone with a previous history of HZ, and those with conditions that might interfere with study evaluations, including people with cognitive impairment, severe hearing loss, those who were non-ambulatory and those whose survival was not considered to be at least 5 years. Randomization was stratified by age, 60-69 and ≥ 70 years of age. All suspected zoster cases were adjudicated by a clinical evaluation committee. Final determination of zoster cases was made by PCR, local culture, or the decision of the clinical evaluation committee, in that order. In both vaccination groups (ZOSTAVAX<sup>®</sup> and placebo), subjects who developed zoster were given famciclovir, and, as necessary, pain medications. Severity of pain was evaluated according to a “worst pain” score on a 0-to-10 scale, using the Zoster Brief Pain Inventory (ZBPI), a validated questionnaire. A score of 3 or higher was considered clinically significant because it correlates with significant interference with Activities of Daily Living (ADL).

ZOSTAVAX<sup>®</sup> significantly reduced the risk of developing zoster compared with placebo. The protective efficacy of ZOSTAVAX<sup>®</sup> against zoster was 51% (95% CI: [44 to 58%], p<0.001).

See CLINICAL TRIALS.

## **STORAGE AND STABILITY**

During shipment, to ensure that there is no loss of potency, ZOSTAVAX<sup>®</sup> II must be maintained at a temperature between -50°C and +8°C. Use of dry ice may subject ZOSTAVAX<sup>®</sup> II to temperatures colder than -50°C.

ZOSTAVAX<sup>®</sup> II **SHOULD BE STORED REFRIGERATED** at a temperature of 2 to 8°C 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) or in the refrigerator (2 to 8°C).

Before reconstitution, protect from light.

**DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.**

**DO NOT FREEZE THE RECONSTITUTED VACCINE.**

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

### **Dosage Forms**

ZOSTAVAX<sup>®</sup> II (zoster vaccine live, attenuated [Oka/Merck], refrigerator-stable) is supplied as a sterile, lyophilized white to off-white compact crystalline plug in a single-dose vial.

The diluent (Sterile Diluent for Merck Sharp & Dohme Corp., live, attenuated, virus vaccines) is a sterile, clear, colourless fluid supplied separately in a single-dose vial.

After reconstitution, ZOSTAVAX<sup>®</sup> II is a semi-hazy to translucent, off-white to pale yellow liquid.

### **Composition**

When reconstituted as directed, each single dose (0.65 mL) contains:

#### **Active Ingredients**

Varicella zoster virus, Oka/Merck strain (live, attenuated)  $\geq 19,400$  PFU\*

\*When reconstituted and stored at room temperature for up to 30 minutes.

#### **Other Ingredients**

##### *Excipients*

Sucrose	41.05 mg
Hydrolyzed porcine gelatin	20.53 mg
Urea	8.55 mg
Sodium chloride	5.25 mg
Monosodium L-glutamate monohydrate	0.82 mg
Sodium phosphate dibasic	0.75 mg
Potassium phosphate monobasic	0.13 mg
Potassium chloride	0.13 mg

The product contains no preservative.

The diluent is sterile water for injection.

*Manufacturing Process Residuals*

The product also contains residual components of MRC-5 cells, and trace quantities of neomycin and bovine calf serum.

**Packaging**

ZOSTAVAX<sup>®</sup> II is supplied in 3 mL single-dose Type I glass vials. Each vial contains one dose of lyophilized vaccine (approximately 0.65 mL when reconstituted as directed).

The diluent (0.7 mL) is supplied separately in 3 mL single-dose Type I glass vials.

The container closure systems of ZOSTAVAX<sup>®</sup> II and the diluent are free of latex.

ZOSTAVAX<sup>®</sup> II is available in packages of 1 and 10 single-dose vials. The diluent is also available in packages of 1 and 10 single-dose vials.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name: Zoster vaccine live, attenuated [Oka/Merck]

#### Product Characteristics

ZOSTAVAX<sup>®</sup> II (zoster vaccine live, attenuated [Oka/Merck], refrigerator-stable) is a lyophilized preparation of the Oka/Merck strain of live, attenuated varicella-zoster virus (VZV). Before reconstitution, it is a white to off-white compact crystalline plug. The diluent (sterile water for injection) is clear and colourless. When reconstituted as directed, ZOSTAVAX<sup>®</sup> II 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 varicella-zoster virus when reconstituted and stored at room temperature for up to 30 minutes. The product contains no preservative.

### CLINICAL TRIALS

#### Study demographics and trial design

**Table 5**  
**Summary of patient demographics for clinical trials**

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Age (years)
004	Randomized, double-blind, placebo-controlled study	ZOSTAVAX <sup>®</sup> frozen formulation or placebo Dosage: 0.5 mL Route of administration: subcutaneous Duration: ZOSTAVAX <sup>®</sup> frozen formulation on Day 0 or placebo on Day 0	38,546	59 - 99
022	Randomized, double-blind, placebo-controlled, multicenter study	ZOSTAVAX <sup>®</sup> frozen formulation or placebo Dosage: 0.65 mL Route of administration: subcutaneous Duration: ZOSTAVAX <sup>®</sup> frozen formulation on Day 1 or placebo on Day 1	22,439	50-59
007	Randomized, double-blind, placebo-controlled, multicenter study	ZOSTAVAX <sup>®</sup> frozen formulation or placebo Dosage: two 0.5 mL Route of administration: subcutaneous Duration: ZOSTAVAX <sup>®</sup> frozen formulation on Day 0 and Day 42 or placebo on Day 0 and Day 42	209	58-90
009	Randomized, controlled, double-blind study	ZOSTAVAX <sup>®</sup> frozen formulation (high dose or low dose) Dosage: 0.65 mL Route of administration: subcutaneous Duration: ZOSTAVAX <sup>®</sup> frozen formulation (high dose or low dose) on Day 0	698	50-90

**Table 5**  
**Summary of patient demographics for clinical trials**

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Age (years)
010	Randomized, controlled, double-blind study	ZOSTAVAX <sup>®</sup> frozen formulation or ZOSTAVAX <sup>®</sup> II refrigerator-stable formulation Route of administration: subcutaneous Duration: ZOSTAVAX <sup>®</sup> frozen formulation on Day 1 or ZOSTAVAX <sup>®</sup> II refrigerator-stable formulation on Day 1	367	50-88

Evaluation of Clinical Efficacy Afforded by ZOSTAVAX<sup>®</sup>

**ZOSTAVAX<sup>®</sup> Efficacy and Safety Trial (ZEST) in Subjects 50 to 59 Years of Age**

In the ZOSTAVAX<sup>®</sup> Efficacy and Safety Trial (ZEST), a placebo-controlled, double-blind clinical trial, 22,439 subjects 50 to 59 years of age were randomized to receive a single dose of either ZOSTAVAX<sup>®</sup> (n=11,211) or placebo (n=11,228) and were followed for the development of zoster for a median of 1.3 years (range 0 to 2 years). All suspected zoster cases were adjudicated by a clinical evaluation committee. Final determination of zoster cases was made by PCR [86%], or in the absence of virus detection, as determined by a clinical evaluation committee [14%].

ZOSTAVAX<sup>®</sup> significantly decreased the incidence of zoster compared with placebo (30 cases [2.0/1000 person-years] vs. 99 cases [6.6/1000 person-years], respectively; p<0.001). The protective efficacy of ZOSTAVAX<sup>®</sup> against zoster was 69.8% (95% CI: [54.1 to 80.6%]).

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

In the Shingles Prevention Study (SPS), a placebo-controlled, double-blind clinical trial of ZOSTAVAX<sup>®</sup> frozen formulation, 38,546 subjects 60 years of age or older were randomized to receive a single dose of either ZOSTAVAX<sup>®</sup> (n=19,270) or placebo (n=19,276) and were followed for the development of zoster for a median of 3.1 years (range 31 days to 4.9 years). The study excluded people who were immunocompromised, anyone with a previous history of HZ, and those with conditions that might interfere with study evaluations, including people with cognitive impairment, severe hearing loss, those who were non-ambulatory and those whose survival was not considered to be at least 5 years. Randomization was stratified by age, 60-69 and ≥ 70 years of age. All suspected zoster cases were adjudicated by a clinical evaluation committee. Final determination of zoster cases was made by PCR, local culture, or the decision of the clinical evaluation committee, in that order. In both vaccination groups (ZOSTAVAX<sup>®</sup> and placebo), subjects who developed zoster were given famciclovir, and, as necessary, pain medications. Severity of pain was evaluated according to a “worst pain” score on a 0-to-10 scale, using the Zoster Brief Pain Inventory (ZBPI), a validated questionnaire. A score of 3 or higher was considered clinically significant because it correlates with significant interference with activities of daily living (ADL).

ZOSTAVAX<sup>®</sup> significantly decreased the incidence of zoster compared with placebo (315 cases [5.4/1000 person-years] vs. 642 cases [11.1/1000 person-years], respectively;  $p < 0.001$ ). The protective efficacy of ZOSTAVAX<sup>®</sup> against zoster was 51% (95% CI: [44 to 58%]).

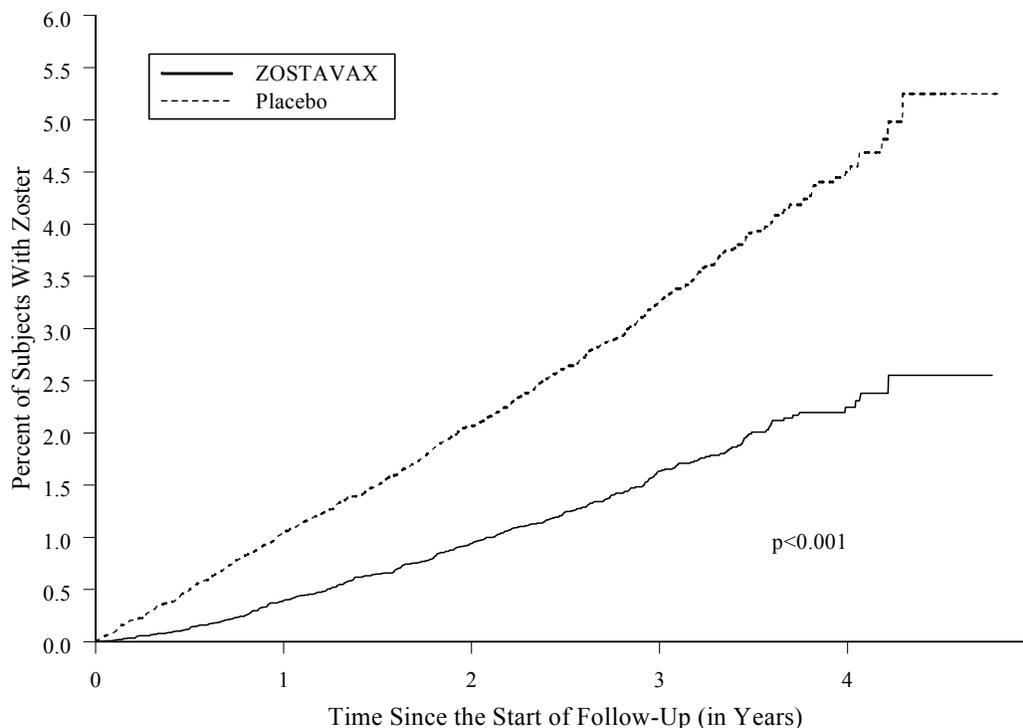
**Table 6**  
**Efficacy of ZOSTAVAX<sup>®</sup> on HZ Incidence Compared with Placebo in the Shingles Prevention Study\***

Age group (yrs.)	ZOSTAVAX <sup>®</sup>			Placebo			Vaccine Efficacy (95% CI)
	# subjects	# HZ cases	Incidence rate of HZ per 1000 person-yrs.	# subjects	# HZ cases	Incidence rate of HZ per 1000 person-yrs.	
Overall	19254	315	5.4	19247	642	11.1	51% (44%, 58%)
60-69	10370	122	3.9	10356	334	10.8	64% (56%, 71%)
≥ 70	8884	193	7.2	8891	308	11.5	38% (25%, 48%)

\*The analysis was performed on the Modified Intent-To-Treat (MITT) population that included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of HZ within the first 30 days postvaccination.

ZOSTAVAX<sup>®</sup> reduced the incidence of zoster by 64% (95% CI: [56 to 71%]) in individuals 60-69 years of age and by 38% (95% CI: [25 to 48%]) in individuals ≥ 70 years of age. The cumulative incidence of zoster over time among vaccine recipients was also significantly reduced ( $p < 0.001$ ; Figure 1). The duration of protection against herpes zoster beyond 4 years is unknown.

**Figure 1**  
**Kaplan-Meier Plot of the Cumulative Incidence of Zoster Over Time\* in the Shingles Prevention Study**



\*A limited number of subjects were followed beyond Year 4.

ZOSTAVAX<sup>®</sup> decreased the incidence of PHN compared with placebo in subjects who experienced zoster, despite vaccination (27 cases [8.6% of HZ cases] vs. 80 cases [12.5% of HZ cases]). In this trial, the definition of PHN was clinically significant zoster-associated pain persisting or appearing at least 90 days after the onset of rash (see Table 7).

**Table 7**  
**Postherpetic Neuralgia (PHN) in the Shingles Prevention Study\***

Age Group (Years)	ZOSTAVAX <sup>®</sup>				Placebo				Vaccine efficacy against PHN in subjects who developed HZ at least 30 days post-vaccination (95% CI)
	Number of Subjects	Number PHN Cases	Number of HZ Cases	HZ cases with PHN (%)	Number of Subjects	Number of PHN Cases	Number of HZ Cases	HZ cases with PHN (%)	
60-69	10370	8	122	6.6	10356	23	334	6.9	5% (-107%, 56%)
≥ 70	8884	19	193	9.8	8891	57	308	18.5	47% (13%, 67%)
Overall	19254	27	315	8.6	19247	80	642	12.5	39% (7%, 59%)

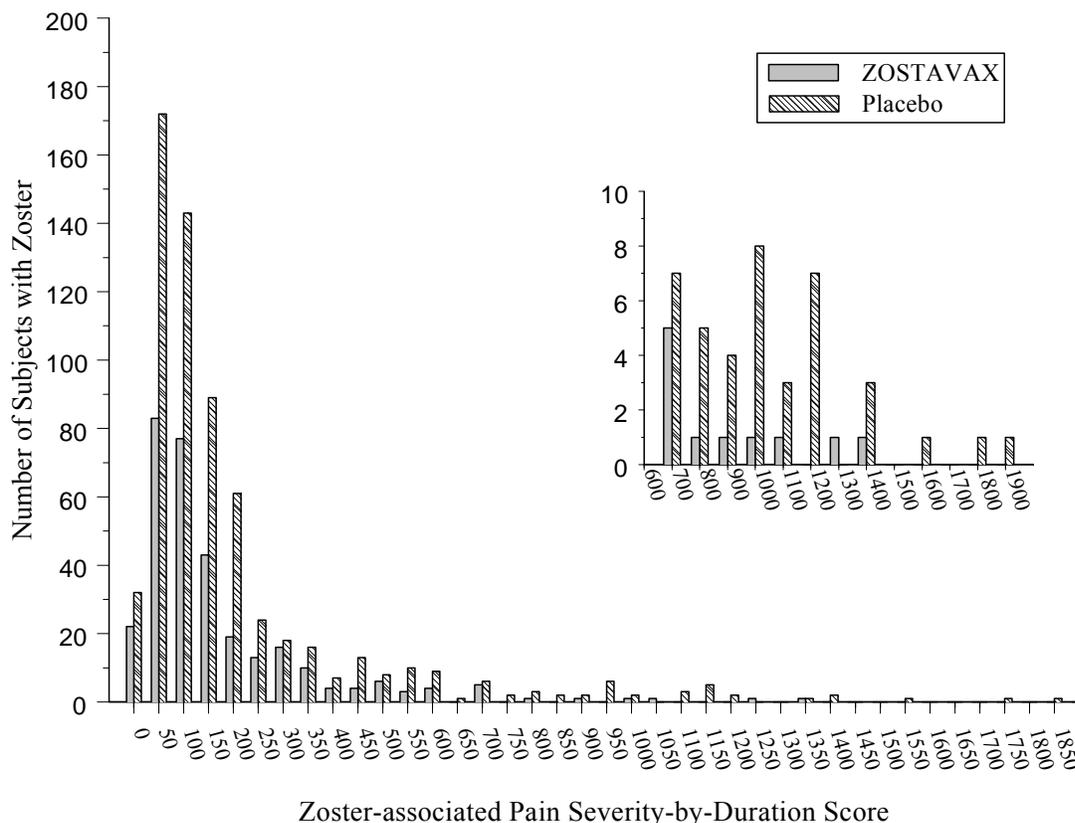
\*The analysis was performed on the Modified Intent-To-Treat (MITT) population which included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of HZ within the first 30 days postvaccination.

The duration of protection against PHN beyond 4 years is unknown. In a limited extension of the SPS, the estimated vaccine efficacy against PHN did not reach statistical significance. A longer term follow-up study, The Long Term Persistence Study, is being undertaken.

ZOSTAVAX<sup>®</sup> reduced the incidence of severe and long-lasting zoster-associated pain (severity-by-duration score >600) by 73% (95% CI: [46 to 87%]) compared with placebo. Eleven subjects vaccinated with ZOSTAVAX<sup>®</sup> had severity-by-duration scores >600, compared with 40 subjects who received placebo (see Figure 2).

Among vaccinated individuals who developed zoster, ZOSTAVAX<sup>®</sup> significantly reduced zoster-associated pain compared with placebo. Over the 6-month follow-up period, there was a 22% reduction in the severity-by-duration score (average scores of 141 for ZOSTAVAX<sup>®</sup> and 181 for placebo; p=0.008). The duration of protection against zoster-associated pain beyond 4 years is unknown.

Figure 2  
Zoster-associated Pain Severity-by-Duration Score Over Time in the Shingles Prevention Study\*



\*The inset presents the number of subjects with severity-by-duration score >600. For example, a daily worst pain rated at the maximum score of 10 for >60 days would result in a severity-by-duration score of >600.

Among vaccinated individuals who developed PHN, ZOSTAVAX<sup>®</sup> significantly reduced PHN-associated pain compared with placebo. In the period from 90 days after rash onset to the end of follow-up, there was a 57% reduction in the severity-by-duration score (average scores of 347 for ZOSTAVAX<sup>®</sup> and 805 for placebo; p=0.016).

Fewer complications were reported by subjects who received ZOSTAVAX<sup>®</sup> compared with subjects who received placebo. The number of subjects with specific complications of zoster that were reported in the SPS at a frequency of ≥ 1% is shown in Table 8.

**Table 8**  
**Number of Subjects with Specific Complications\* of Zoster among HZ cases that were Reported in the Shingles Prevention Study**

Complication	ZOSTAVAX <sup>®</sup> (N = 19,270)		Placebo (N = 19,276)	
	(n = 321)	% Among Zoster Cases	(n = 659)	% Among Zoster Cases
Allodynia	135	42.1	310	47.0

**Table 8**  
**Number of Subjects with Specific Complications\* of Zoster among HZ cases**  
**that were Reported in the Shingles Prevention Study**

Complication	ZOSTAVAX <sup>®</sup> (N = 19,270)		Placebo (N = 19,276)	
	(n = 321)	% Among Zoster Cases	(n = 659)	% Among Zoster Cases
Bacterial Superinfection	3	0.9	7	1.1
Dissemination	5	1.6	11	1.7
Impaired Vision	2	0.6	9	1.4
Ophthalmic Zoster	35	10.9	69	10.5
Peripheral Nerve Palsies (motor)	5	1.6	12	1.8
Ptosis	2	0.6	9	1.4
Scarring	24	7.5	57	8.6
Sensory Loss	7	2.2	12	1.8

N=number of subjects randomized

n=number of zoster cases, including those cases occurring within 30 days postvaccination, with these data available

\*Complications reported at a frequency of  $\geq 1\%$  in at least one vaccination group among subjects with zoster.

Visceral complications such as pneumonitis, hepatitis, and meningoencephalitis were reported by fewer than 1% of subjects with zoster (3 cases of pneumonitis and 1 case of hepatitis in the placebo group; 1 case of meningoencephalitis in the vaccine group).

#### Immunogenicity of ZOSTAVAX<sup>®</sup>

Within the ZOSTAVAX<sup>®</sup> Efficacy and Safety Trial (ZEST), immune responses to vaccination were evaluated in a random 10% subcohort (n=1,136 for ZOSTAVAX<sup>®</sup> and n=1,133 for placebo) of the subjects enrolled in the ZEST. ZOSTAVAX<sup>®</sup> elicited higher VZV-specific immune responses at 6 weeks postvaccination compared with placebo. Increases in VZV antibody level, measured by glycoprotein enzyme-linked immunosorbent assay (gpELISA) were demonstrated (2.3-fold difference (95% CI [2.2, 2.4]), geometric mean titer [GMT] of 664 vs 289 gpELISA units/mL, p<0.001).

Within the Shingles Prevention Study (SPS), immune responses to vaccination were evaluated in a subset of the enrolled subjects (N=1395). ZOSTAVAX<sup>®</sup> elicited higher VZV-specific immune responses at 6 weeks postvaccination compared with placebo. Increases in both VZV antibody level, measured by gpELISA (1.7 fold-difference, geometric mean titer [GMT] of 479 vs. 288 gpELISA units/mL, p <0.001), and T-cell activity, measured by VZV interferon-gamma enzyme-linked immunospot (IFN- $\gamma$  ELISPOT) assay (2.2 fold-difference, geometric mean count [GMC] of 70 vs. 32 spot-forming cells per million peripheral blood mononuclear cells [SFC/10<sup>6</sup> PBMCs], p<0.001) were demonstrated. The specific antibody level that correlates with protection from zoster has not been established.

A randomized, controlled, double-blind study (P010), conducted in adults  $\geq 50$  years of age, compared the safety, tolerability, and immunogenicity of ZOSTAVAX<sup>®</sup> frozen formulation with that of ZOSTAVAX<sup>®</sup> II refrigerator-stable formulation. Subjects were randomized in a 1:1 ratio to receive either ZOSTAVAX<sup>®</sup> frozen (N=185) or ZOSTAVAX<sup>®</sup> II refrigerator-stable (N=183). At 4 weeks postvaccination, the VZV antibody response induced by ZOSTAVAX<sup>®</sup> II was similar

(noninferior) to that induced by ZOSTAVAX<sup>®</sup> (estimated GMT ratio of ZOSTAVAX<sup>®</sup> II /ZOSTAVAX<sup>®</sup> = 0.87 (95% CI: [0.71 to 1.07], meeting the pre-specified criterion). The VZV antibody responses induced by ZOSTAVAX<sup>®</sup> II and by ZOSTAVAX<sup>®</sup> were found to be acceptable; the estimated GMFR of the VZV antibody response at 4 weeks postvaccination was 2.6 (95% CI: 2.2 to 3.0) in the ZOSTAVAX<sup>®</sup> II group and 2.9 (95% CI: 2.4 to 3.4) in the ZOSTAVAX<sup>®</sup> group.

#### Immunogenicity Following Concomitant Administration

In a double-blind, controlled clinical trial, 473 adults, 60 years of age or older, were randomized to receive ZOSTAVAX<sup>®</sup> II and PNEUMOVAX<sup>®</sup> 23 concomitantly (N = 237) or PNEUMOVAX<sup>®</sup> 23 alone followed 4 weeks later by ZOSTAVAX<sup>®</sup> II alone (N = 236). At four weeks postvaccination, the VZV antibody levels following concomitant use were significantly lower than the VZV antibody levels following nonconcomitant administration (GMTs of 338 vs. 484 gpELISA units/mL, respectively; GMT ratio = 0.70 (95% CI: [0.61, 0.80])). VZV antibody levels 4 weeks postvaccination were increased 1.9-fold (95% CI: [1.7, 2.1]; meeting the pre-specified acceptance criterion) in the concomitant group vs. 3.1-fold (95% CI: [2.8, 3.5]) in the nonconcomitant group. The GMTs for PNEUMOVAX<sup>®</sup> 23 antigens were comparable between the two groups. Concomitant use of ZOSTAVAX<sup>®</sup> II and PNEUMOVAX<sup>®</sup> 23 demonstrated a safety profile that was generally similar to that of the two vaccines administered nonconcomitantly.

#### Immunogenicity in subjects on chronic/maintenance systemic corticosteroids

Descriptive study P017 is an estimation study with no hypothesis testing. In this double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX<sup>®</sup> was administered to 206 subjects 60 years of age or older who were receiving chronic/maintenance systemic corticosteroid therapy at a daily dose equivalent of 5 to 20 mg of prednisone for at least 2 weeks prior to enrollment, and 6 weeks or more following vaccination to assess the immunogenicity and safety profile of ZOSTAVAX<sup>®</sup>. Compared with placebo, ZOSTAVAX<sup>®</sup> induced a higher VZV-specific gpELISA antibody GMT at 6 weeks postvaccination (GMT of 531.1 vs. 224.3 gpELISA units/ml, respectively). The geometric mean fold-rise of the VZV antibody response, as measured by gpELISA, from prevaccination to postvaccination was 2.3 (95% CI: [2.0 to 2.7]) in the ZOSTAVAX<sup>®</sup> group compared to 1.1 (95% CI: [1.0 to 1.2]) in the placebo group (see CONTRAINDICATIONS regarding corticosteroids).

#### Immunogenicity in subjects with HIV infection

In a double-blind, placebo-controlled randomized clinical trial, ZOSTAVAX<sup>®</sup> 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/ $\mu$ L). Although a two-dose regimen was used in this study, ZOSTAVAX is administered as a single dose regimen (see DOSAGE AND ADMINISTRATION). In this study, a total of 295 subjects received dose 1 and 286 subjects received dose 2. Compared with placebo, ZOSTAVAX<sup>®</sup> 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.)

#### Immunogenicity and Safety in Subjects Receiving a Booster Dose

In an open-label study, ZOSTAVAX<sup>®</sup> was administered as: (1) a booster dose to 201 HZ history-negative subjects 70 years of age or older who had received a first dose approximately 10 years previously as participants in the SPS, and (2) a first dose to 199 HZ history-negative subjects 70 years of age or older who had not received ZOSTAVAX<sup>®</sup> previously. The antibody response to vaccine 6 weeks postvaccination as measured by gpELISA was similar in the booster dose and first dose group (GMT of 389.1 vs 368.8 gpELISA units/mL, respectively). The geometric mean fold-rise of the VZV antibody response, as measured by gpELISA, from prevaccination to Week 6 postvaccination was 1.5 (95% CI: [1.4 to 1.6]) in both groups.

To evaluate the adverse experiences temporally associated with study vaccination, subjects were given a Vaccination Report Card (VRC) to record any injection-site adverse experiences, systemic adverse experiences, elevated temperatures, and rashes from Days 1 to 42 postvaccination. Subjects were followed for serious adverse experiences, regardless of whether the event was related to the study vaccine, throughout the course of the study (through Day 365). The vaccine was generally well tolerated; the frequency of vaccine-related adverse experiences after the booster dose of ZOSTAVAX<sup>®</sup> was generally similar to that seen with the first dose.

## **TOXICOLOGY**

ZOSTAVAX<sup>®</sup> II has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility.

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**PART III: CONSUMER INFORMATION**

**ZOSTAVAX® II**

(zoster vaccine live, attenuated [Oka/Merck], refrigerator-stable)

This leaflet is part III of a three-part "Product Monograph" published when ZOSTAVAX® II was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ZOSTAVAX® II. Contact your doctor or pharmacist if you have any questions about the vaccine.

**ABOUT THIS VACCINE**

What the vaccine is used for:

ZOSTAVAX® II is indicated for the prevention of shingles (zoster).

ZOSTAVAX® II is indicated for vaccination of individuals 50 years of age or older.

ZOSTAVAX® II boosts your immune system to help protect you from shingles.

ZOSTAVAX® II cannot be used to treat existing shingles or the pain associated with existing shingles.

What it does:

Your doctor has recommended or administered ZOSTAVAX® II to prevent shingles (also known as zoster).

If you do get shingles even though you have been vaccinated, ZOSTAVAX® II can reduce the intensity and length of time your pain from shingles will last.

When it should not be used:

- if you are allergic to any of the components of the vaccine (see ingredients), including gelatin or neomycin
- if you have a blood disorder or any type of cancer that weakens your immune system
- if you have been told by your doctor that you have a weakened immune system as a result of a disease, medications, or other treatment
- if you have active untreated tuberculosis
- if you are pregnant (see **Pregnancy**)

What the medicinal ingredient is:

Active ingredient: a weakened form of the varicella-zoster virus

What the important nonmedicinal ingredients are:

**Powder:**

Sucrose, hydrolyzed porcine gelatin, urea, sodium chloride, potassium dihydrogen phosphate, potassium chloride, monosodium L-glutamate and anhydrous disodium phosphate.

**Solvent:**

Water for injection

What dosage forms it comes in:

ZOSTAVAX® II is supplied as a white to off-white powder in a single-dose vial.

The diluent for reconstitution is supplied as a clear, colourless liquid in a single-dose vial.

When reconstituted, ZOSTAVAX® II is a semi-hazy to translucent, off-white to pale yellow liquid.

**WARNINGS AND PRECAUTIONS**

BEFORE you use ZOSTAVAX® II talk to your doctor or pharmacist if:

- you have or have had any medical problems and about any allergies
- you are taking or have taken any medications that might weaken your immune system
- you have a fever
- you have HIV infection
- you have had shingles in the past.

It is not known how long ZOSTAVAX® II will protect you from shingles. Studies with ZOSTAVAX® II beyond 4 years have not been completed. It is not known if you will need to be vaccinated again in the future.

ZOSTAVAX® II does not protect all individuals against the development of shingles or its consequences.

There may be a small chance of spreading the weakened vaccine virus to other people after receiving ZOSTAVAX® II.

**Pregnancy**

ZOSTAVAX® II should not be given to pregnant women. Women of child-bearing age should take the necessary precautions to avoid pregnancy for 3 months following vaccination.

Ask the doctor or pharmacist for advice before taking any medicine.

**Breast-feeding**

Inform your doctor if you are breast-feeding or intending to breast-feed. Your doctor will decide if ZOSTAVAX® II should be given.

Ask the doctor or pharmacist for advice before taking any medicine.

**Driving and using machines:**

There is no information to suggest that ZOSTAVAX® II affects the ability to drive or operate machinery.

**INTERACTIONS WITH THIS VACCINE**

**Important information about the ingredients of ZOSTAVAX® II:**

Tell your doctor if you have ever had an allergic reaction to any of the ingredients before you receive this vaccine.

**Using other medicines and other vaccines:**

ZOSTAVAX® II should not be given at the same time as PNEUMOVAX® 23 (pneumococcal vaccine, polyvalent, MSD Std.). For more information about these vaccines, talk to your doctor or healthcare provider because it may be better to get these vaccines at least 4 weeks apart.

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

**PROPER USE OF THIS VACCINE**

Usual dose:

Individuals should receive a single dose.

The vaccine is to be given as a single dose by injection under the skin.

ZOSTAVAX® II is not a treatment for shingles or the pain associated with shingles. If you get shingles, even though you have been vaccinated, see your health care provider promptly.

It is recommended that the vaccine be administered immediately after reconstitution to minimize loss of potency. Discard if reconstituted vaccine is not used within 30 minutes.

**Do not freeze the reconstituted vaccine.**

**DO NOT INJECT INTRAVASCULARLY.**

Any unused product or waste material should be disposed of in accordance with local requirements.

Overdose:

There are no data with regard to overdose.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Not applicable

**HOW TO STORE IT**

Keep this vaccine out of the reach and sight of children.

Vial of powder: Store and transport refrigerated at 8°C or colder (especially when taken from the pharmacy to the physician’s office) and keep the vial in the outer carton in order to protect from light.

Diluent: Store separately from the vaccine vial in a refrigerator (2 to 8°C) or at room temperature (20 to 25°C). Do not freeze.

Do not use after the expiry date stated on the label.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Like all vaccines, ZOSTAVAX® II can have side effects.

In studies, the most common side effects reported were at the injection site. These side effects included redness, pain, swelling, hard lump, itching, warmth, and bruising at the injection site. Headache and pain in an arm or leg were also reported.

The following additional side effects have been reported with ZOSTAVAX® II:

- allergic reactions, which may be serious and may include difficulty in breathing or swallowing. If you have an allergic reaction, call your doctor right away
- chicken pox
- fever
- hives at the injection site
- joint pain
- muscle pain
- nausea
- rash
- rash at the injection site
- shingles
- swollen glands near the injection site (that may last a few days to a few weeks)

Your doctor or pharmacist has a more complete list of side effects for ZOSTAVAX® II.

If you noticed any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

If any of the conditions above persists or worsens, seek medical attention.

**Reporting Suspected Vaccine Adverse Events**

**For the general public:**

If you suspect you have had a serious or unexpected event following receipt of a vaccine, please ask your healthcare professional to complete the Adverse Events Following Immunization (AEFI) Form and send it to your local [health unit](#) in your province/territory.

**For healthcare professionals:**

If a patient experiences an adverse event following immunization, please complete the Adverse Events Following Immunization (AEFI) Form and send it to your local [health unit](#) in your province/territory.

If you have any questions or have difficulty contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

Toll-free telephone: 1-866-844-0018  
 Toll-free fax: 1-866-844-5931  
 By email: [caefi@phac-aspc.gc.ca](mailto:caefi@phac-aspc.gc.ca)

*NOTE: Should you require information related to the management of the adverse events, please contact your health professional before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.*

**MORE INFORMATION**

**Disease information on shingles:**

**Why should I receive ZOSTAVAX® II?**

Shingles can be a very painful and potentially debilitating disease. Shingles can cause long-lasting nerve pain and other serious complications. It is an unpredictable disease that can occur at any time, with no warning. Almost every adult has had chickenpox and so is at risk for shingles. The risk increases as you get older. This is especially true if you are over 50 years of age. ZOSTAVAX® II is the only product approved to prevent shingles. If you do get shingles even though you have been vaccinated, ZOSTAVAX® II can help reduce the intensity and length of time your nerve pain will last.

**What is shingles?**

Shingles is a painful, blistering rash. It usually occurs in one part of the body and can last for several weeks. It may result in scarring. The nerve pain that comes from shingles can last for months or even years after the rash heals.

**What causes shingles?**

Shingles is caused by the same virus that causes chickenpox. After your chickenpox blisters heal, the virus that caused them stays in your body in nerve cells. The virus may be there for many years and not cause a problem. Sometimes, for unknown reasons, it becomes active again and causes shingles.

**Is shingles serious?**

Shingles can be serious. In addition to the rash-associated pain, the nerve pain caused by shingles may be severe and last for months or years (postherpetic neuralgia). For some people, this nerve pain can get in the way of normal day-to-day activities such as walking, sleeping, and social activities. The pain from shingles can also lead to emotional distress. People who suffer from shingles have described their pain in many ways. Some say the pain burns or throbs. Others say it stabs, shoots, and/or feels sharp. Severe pain can result from things as minor as a breeze or the touch of clothing against the skin.

In addition to severe pain, people with shingles may have other complications. These include:

- scarring
- bacterial skin infections
- weakness
- muscle paralysis
- loss of hearing or vision.

Shingles can result in hospitalization. In rare cases, shingles can even result in death.

**Am I at risk for shingles?**

Almost every adult has had chickenpox and so is at risk for shingles. The risk increases as you get older, especially if you are over 50 years of age. It is estimated that in the general population, the lifetime risk of getting shingles is as high as 30%. For people who reach 85 years of age, one out of every two will have had shingles.

**If you want more information about ZOSTAVAX® II:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the [Health Canada website](#) or Merck Canada website [www.merck.ca](http://www.merck.ca). or by calling Merck Canada at 1-800-567-2594

To report an adverse event related to ZOSTAVAX® II, please contact 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

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