PRODUCT CIRCULAR

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

I. THERAPEUTIC CLASS

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

II. INDICATIONS

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

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

III. 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.

Prefilled syringe of diluent:

To reconstitute the vaccine, inject all 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.

IV. 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 may result in disseminated disease in individuals who are immunosuppressed or immunodeficient.

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 **XIV. CLINICAL PHARMACOLOGY** and **XI. ADVERSE EVENTS**); cellular immune deficiencies.

Immunosuppressive therapy (including high-dose corticosteroids) (see **XI. ADVERSE EVENTS**); 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 **VI. PREGNANCY**).

V. PRECAUTIONS

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

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 (see **IV. CONTRAINDICATIONS**). However, a phase II safety and immunogenicity study in HIV-infected adults with conserved immune function has been completed (see **XIV. CLINICAL PHARMACOLOGY** and **XI. ADVERSE EVENTS**).

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.

VI. 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 **IV. CONTRAINDICATIONS**).

VII. 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.

VIII. PEDIATRIC USE

ZOSTAVAX is not recommended for use in this age group.

IX. 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.

X. 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.

Use with other vaccines

ZOSTAVAX can be administered concomitantly with inactivated influenza vaccine using separate syringes (see Dosage and Administration).

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

XI. ADVERSE EVENTS

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 (≥ 1/10) and common (≥ 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 postvaccination 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.

Of reported varicella-like rashes (n=124, 69 for ZOSTAVAX 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; 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 (≥ 1/10) and common (≥ 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.

In an open-label study, ZOSTAVAX was administered as 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, and as a first dose to 199 HZ history-negative subjects 70 years of age or older. The vaccine was generally well tolerated; the frequency of vaccine-related adverse experiences after the booster dose of ZOSTAVAX was generally similar to that seen with the first dose.

Immunogenicity in subjects on chronic/maintenance systemic corticosteroids

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX 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. 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 **IV. CONTRAINDICATIONS** regarding corticosteroids)

Immunogenicity in HIV-infected adults with conserved immune function

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 ≥ 200 cells/μL). Although a two-dose regimen was used in this study, ZOSTAVAX is administered as a single dose regimen (See **III. 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). One case of serious vaccine related maculo-papular rash was reported on Day 4 following Dose 1 of ZOSTAVAX. In this clinical trial, the safety profile was generally similar to that seen in the Adverse Event Monitoring Substudy of the SPS. (See **IV. 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 sites 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)

XII. INCOMPATIBILITIES

See **X. DRUG INTERACTIONS.**

XIII. OVERDOSAGE

There are no data with regard to overdose.

XIV. CLINICAL PHARMACOLOGY

Pharmacotherapeutic group: Viral Vaccine
ATC code: J07BK02

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 in Europe (585 million population in 2005), where an estimated 2.1 million cases occur every year. This number is expected to rise with the aging of the population. 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. It is estimated that by 85 years of age, 50% of individuals will have experienced an episode of zoster. Available hospitalization data for zoster are limited in Europe. 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 postherpetic neuralgia (PHN), scarring, bacterial superinfection, motor neuron palsies, pneumonia, encephalitis, Ramsay Hunt Syndrome, visual impairment, hearing loss, and death.

Zoster-associated pain and discomfort can be prolonged and disabling and can diminish quality of life and functional capacity to a degree comparable to such debilitating diseases as congestive heart failure, myocardial infarction, type II diabetes mellitus, and major depression.

Postherpetic Neuralgia

Postherpetic neuralgia (PHN) constitutes the most common serious complication and cause of zoster-associated morbidity in the immunocompetent host. Based on extrapolation of published prevalence data, the prevalence of PHN is estimated to be 1 to 2 million cases in Europe (585 million population). The frequency and severity of PHN increase with age, and may complicate 25 to 50% of zoster cases

among patients over 50 years of age. 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 types 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.

Mechanism of Action

The risk of developing zoster appears to be causally related to a decline in VZV-specific immunity. ZOSTAVAX was shown to boost VZV-specific immunity, which is thought to be the mechanism by which it protects against zoster and its complications. (See *Immunogenicity*.)

Clinical Studies

Evaluation of Clinical Efficacy Afforded by ZOSTAVAX

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

In the ZOSTAVAX Efficacy and Safety Trial (ZEST), a placebo-controlled, double-blind clinical trial in which 22,439 subjects 50 to 59 years of age were randomized to receive a single dose of either ZOSTAVAX (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 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 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, 38,546 subjects 60 years of age or older were randomized to receive a single dose of either ZOSTAVAX (n=19,270) or placebo (n=19,276) and were followed for the development of zoster for an average of 3.1 years (range 1 day to 4.9 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 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).

As shown in Table 1, ZOSTAVAX significantly reduced the risk of developing zoster and PHN compared with placebo. In addition, ZOSTAVAX significantly reduced acute and chronic zoster-associated pain as measured by the HZ pain Burden of Illness (BOI) score (see definition in Table 1).

Table 1
Efficacy of ZOSTAVAX Compared with Placebo
in the Shingles Prevention Study

Endpoint	Vaccine efficacy	95% CI
Incidence of Zoster	51%	44 to 58%
Incidence of PHN*	67%	48 to 79%
HZ Pain BOI**	61%	51 to 69%

*Clinically significant zoster-associated pain persisting or appearing at least 90 days after the onset of rash.

**The HZ pain BOI score is a composite score that incorporates the incidence, severity, and duration of acute and chronic zoster-associated pain over a 6-month follow-up period.

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

In the SPS, the reduction in zoster was seen in almost all dermatomes. Ophthalmic zoster occurred in 35 subjects vaccinated with ZOSTAVAX vs. 69 subjects who received placebo. Impaired vision occurred in 2 subjects vaccinated with ZOSTAVAX vs. 9 who received placebo.

ZOSTAVAX decreased the incidence of PHN compared with placebo [(27 cases [0.5/1000 person-years] vs. 80 cases [1.4/1000 person-years], respectively; $p<0.001$). 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.

The protective efficacy of ZOSTAVAX against PHN was 67% (95% CI: [48 to 79%]), and the reduction was similar for the two age groups (60-69 and ≥ 70 years of age). In addition, the efficacy of ZOSTAVAX did not change appreciably when PHN was defined using alternative cutoff times (30, 60, 120, or 182 days) for duration of pain. ZOSTAVAX significantly reduced the cumulative incidence of PHN over time compared with placebo ($p<0.001$).

ZOSTAVAX reduced the HZ pain BOI score by approximately 61% (95% CI: [51 to 69%]), compared with placebo. ZOSTAVAX reduced the HZ pain BOI score to a similar extent for the two age groups (60-69 and ≥ 70 years of age). The HZ pain BOI score is a composite score that incorporates the incidence, severity, and duration of acute and chronic zoster-associated pain over a 6-month follow-up period.

ZOSTAVAX reduced the incidence of zoster with severe and long-lasting pain (severity-by-duration score >600) by 73% (95% CI: [46 to 87%]) compared with placebo. Eleven subjects vaccinated with ZOSTAVAX had severity-by-duration scores >600 compared with 40 subjects who received placebo. 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 zoster, ZOSTAVAX 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 and 181 for placebo, $p=0.008$).

Among vaccinated individuals who developed PHN, ZOSTAVAX 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 and 805 for placebo; $p=0.016$).

To evaluate the impact of ZOSTAVAX on ADL interference associated with zoster, a combined score was calculated for each subject based on interference with general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life. Each item was measured on a 0-to-10 scale (0 being no interference and 10 being maximum interference). Compared to placebo, ZOSTAVAX led to a favorable, but not statistically significant, reduction (8.2%) in the risk of having substantial ADL interference (defined as having a combined ADL interference score ≥ 2 for ≥ 7 days) beyond the vaccine efficacy for zoster.

Among vaccinated individuals who developed zoster, ZOSTAVAX significantly reduced ADL interference compared with placebo. Over the 6-month follow-up period, there was a 31% reduction in the severity-by-

duration score for combined ADL interference (average scores of 57 for ZOSTAVAX and 83 for placebo; p=0.002).

The use of antiviral drugs within 72 hours of zoster rash onset did not have a significant effect on the efficacy of ZOSTAVAX for zoster pain or PHN incidence. The proportions of subjects using medications with analgesic effects were balanced between vaccination groups. Therefore, the use of these medications was not likely to have contributed to the reduction of zoster pain or PHN incidence.

Immunogenicity of ZOSTAVAX

Within the ZOSTAVAX Efficacy and Safety Trial (ZEST), immune responses to vaccination were evaluated in a random 10% subcohort (n=1,136 for ZOSTAVAX and n=1,133 for placebo) of the subjects enrolled in the ZEST. ZOSTAVAX 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. 288 gpELISA units/mL, p <0.001); the specific antibody level that correlates with individual protection from zoster has not been established.

Within the Shingles Prevention Study (SPS), immune responses to vaccination were evaluated in a subset of the enrolled subjects (N=1395). ZOSTAVAX elicited higher VZV-specific immune responses at 6 weeks postvaccination compared with placebo. Increases in both VZV antibody level, measured by glycoprotein enzyme-linked immunosorbent assay (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-ɣ ELISPOT) assay (2.2 fold-difference, geometric mean count [GMC] of 70 vs. 32 spot-forming cells per million peripheral blood mononuclear cells [SFC/10^6 PBMCs], p<0.001) were demonstrated.

In an integrated analysis of two clinical trials evaluating immune response to ZOSTAVAX at 4 weeks postvaccination, responses were generally similar in subjects 50 to 59 (N=389) compared to subjects ≥ 60 years of age (N=731) (GMT of 668 vs. 614 gpELISA units/ml, respectively). The geometric mean fold-rise of immune response following vaccination as measured by gpELISA was 2.6-fold (95% CI: [2.4 to 2.9]) in subjects 50 to 59 years of age and 2.3-fold (95% CI: [2.1 to 2.4]) in subjects ≥ 60 years of age.

The SPS Short-term Persistence Substudy (STPS)

The STPS was initiated to accrue additional information on the persistence of vaccine efficacy and to preserve a subset of subjects for the long-term persistence substudy (LTPS). The STPS included 7,320 subjects previously vaccinated with ZOSTAVAX and 6,950 subjects previously vaccinated with placebo in

the SPS. The mean age at enrollment in STPS was 73.3 years. During the course of STPS, placebo recipients were offered ZOSTAVAX, at which time they were considered to have completed the STPS.

The STPS analyses for vaccine efficacy are based on data collected primarily 4 to 7 years postvaccination in the SPS. The median follow-up in the STPS was ~1.2 years (range is one day to 2.2 years). In the STPS, there were 84 evaluable HZ cases in the ZOSTAVAX group and 95 evaluable cases in the placebo group. The estimated vaccine efficacy for HZ incidence during the STPS follow-up period was 39.6% (18.2%, 55.5%). The estimated vaccine efficacy for PHN incidence was 60.1% (-9.8%, 86.7%).The estimated vaccine efficacy for HZ BOI was 50.1% (14.1%, 71.0%).

There were no vaccine-related serious adverse experiences reported in the STPS.

The SPS Long-term Persistence Substudy (LTPS)

Following completion of the STPS, the open-label LTPS evaluated the duration of protection against HZ, PHN and HZ BOI of ZOSTAVAX on subjects vaccinated in the SPS. A total of 6,867 subjects previously vaccinated with ZOSTAVAX in the SPS participated in the LTPS. The mean age at enrollment into LTPS was 74.5 years.

Because placebo subjects were previously offered vaccine during the STPS, a concurrent placebo control group was not available for calculation of vaccine efficacy for the LTPS. Therefore, prior placebo recipients were used as a reference group for calculating vaccine efficacy in the LTPS.

The LTPS analyses for vaccine efficacy are based on data collected primarily from Year 7 through Year 10 following vaccination in the SPS. Median follow up during the LTPS was ~3.9 years (range is one week to 4.75 years). There were 263 evaluable HZ cases during the LTPS. The estimated vaccine efficacy for HZ incidence during the LTPS follow-up period was 21.1% (10.9%, 30.4%). The estimated vaccine efficacy for PHN incidence was 35.4% (8.8%, 55.8%). The estimated vaccine efficacy for HZ BOI was 37.3% (26.7%, 46.4%).

There were no vaccine-related serious adverse experiences reported in the LTPS.

Immunogenicity following concomitant administration

In a double-blind, controlled clinical trial, 762 adults 50 years of age and older were randomized to receive a single dose of ZOSTAVAX administered either concomitantly (N=382) or nonconcomitantly (N=380) with inactivated influenza vaccine. The antibody responses to both vaccines at 4 weeks postvaccination were similar, whether administered concomitantly or nonconcomitantly.

In a double-blind, controlled clinical trial, 473 adults, 60 years of age or older, were randomized to receive ZOSTAVAX and PNEUMOVAX 23 concomitantly (N=237), or PNEUMOVAX 23 alone followed 4 weeks later by ZOSTAVAX 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 23 antigens were comparable between the two groups. Concomitant use of ZOSTAVAX and PNEUMOVAX 23 demonstrated a safety profile that was generally similar to that of the two vaccines administered nonconcomitantly.

Immunogenicity in subjects with a history of herpes zoster (HZ) prior to vaccination

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. ZOSTAVAX induced a significantly higher VZV-specific immune response as measured by gpELISA at 4 weeks postvaccination, compared with placebo (2.1-fold difference (95% CI: [1.5 to 2.9], $p<0.001$, GMT of 812 vs. 393 gpELISA units/ml). VZV antibody responses were generally similar in subjects 50 to 59 compared to subjects ≥ 60 years of age.

Immunogenicity in subjects on chronic/maintenance systemic corticosteroids

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX 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. Compared with placebo, ZOSTAVAX 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 group compared to 1.1 (95% CI: [1.0 to 1.2]) in the placebo group. (See **IV. CONTRAINDICATIONS** regarding corticosteroids)

Immunogenicity in HIV-infected adults with conserved immune function

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 ≥ 200 cells/μL). Although ZOSTAVAX is indicated as a single dose regimen, a two-dose regimen was used (see **III. 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 **IV. CONTRAINDICATIONS** regarding immunosuppression due to HIV/AIDS.) The antibody titers at Week 12 (6 weeks post dose 2) were not significantly different from the titers at Week 6 (6 weeks post dose 1).

Revaccination

The need for, or timing of, revaccination with ZOSTAVAX has not yet been determined. In an efficacy study, the duration of protection was demonstrated through 48 months of follow-up.

Immunogenicity and Safety in Subjects Receiving a Booster Dose

In an open-label study, ZOSTAVAX 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 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 was generally similar to that seen with the first dose.

XV. CHEMISTRY

ZOSTAVAX is a lyophilized preparation of the Oka/Merck strain of live, attenuated varicella-zoster virus (VZV). The virus was initially obtained from a child with naturally-occurring varicella, then introduced into human embryonic lung cell cultures, adapted to and propagated in embryonic guinea pig cell cultures and finally propagated in human diploid cell cultures (WI-38). Further passage of the virus was performed at Merck Research Laboratories (MRL) in human diploid cell cultures (MRC-5) that were free of adventitious

agents. This live, attenuated zoster vaccine is a lyophilized preparation containing sucrose, phosphate, glutamate, and processed gelatin as stabilizers.

XVI. COMPOSITION

XVIa. Active Ingredients

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.

XVIb. Inactive Ingredients

Each 0.65-mL dose contains: 41.05 mg of sucrose, 20.53 mg of hydrolyzed porcine gelatin, 8.55 mg of urea, 5.25 mg of sodium chloride, 0.82 mg of monosodium L-glutamate, 0.75 mg of sodium phosphate dibasic, 0.13 mg of potassium phosphate monobasic, 0.13 mg of potassium chloride; residual components of MRC-5 cells including DNA and protein; and trace quantities of neomycin and bovine calf serum. The product contains no preservative.

XVII. 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 temperatures 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 **III. DOSAGE AND ADMINISTRATION**). The diluent should be stored separately at or below 25°C 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.

XVIII. AVAILABILITY

ZOSTAVAX is supplied as follows:

(1) A combo package of 1 single-dose vial of lyophilized vaccine, and a pre-filled needleless syringe of sterile diluent with separate needles.
(2) A combo package of 10 single-dose vial of lyophilized vaccine, and 10 pre-filled needleless syringe of sterile diluent with separate needles.

Not all presentations may be available locally.

Marketing Authorization Holder in Singapore:
MSD Pharma (Singapore) Pte. Ltd.
150 Beach Road
#31-00, Gateway West
Singapore 189720

Date of Revision: March 2016

MSD