SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SHINGLES (HERPES ZOSTER) VACCINE (LIVE) BP
(Oka/Merck)
Powder and solvent for suspension for injection
0.65 mL Single Dose Vial of powder and single dose sterile diluent syringe/vial (WFI)
Brand Name: ZOSTAVAX®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

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.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZOSTAVAX® is indicated for:

- prevention of herpes zoster (shingles)
- prevention of postherpetic neuralgia (PHN)
- reduction of acute and chronic zoster-associated pain.

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

4.2 Posology and method of 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.

Posology & Methods of administration

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

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

4.3 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.

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 section 4.8 UNDESIRABLE EFFECTS); cellular immune deficiencies.

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

Active untreated tuberculosis

Pregnancy (see **PREGNANCY**)

4.4 Special warnings and precautions for use

The health care provider should question the patient about reactions to a previous dose of any VZV-containing vaccines (see section 4.3 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. A phase II safety and immunogenicity study in HIV-infected adults with conserved immune function has been completed (see section 4.8 UNDESIRABLE EFFECTS).

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

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

4.5 Interaction with other medicinal products and other forms of Interaction

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® and PNEUMOCOCCAL POLYSACCHARIDE VACCINE should not be given concomitantly because concomitant use resulted in reduced immunogenicity of ZOSTAVAX® (see **CLINICAL PHARMACOLOGY****).

4.6 Pregnancy and lactation

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 section 4.3 CONTRAINDICATIONS).
Nursing Mothers: It is not known whether VZV is secreted in human milk. Therefore, because some viruses are secreted in human milk, caution should be exercised if ZOSTAVAX® is administered to a nursing woman.

Pediatric Use: ZOSTAVAX® is not recommended for use in this age group.
Geriatric Use: The mean age of subjects enrolled in the largest (N=38,546) clinical study of ZOSTAVAX® was 69 years (range 59-99 years). Of the 19,270 subjects who received ZOSTAVAX®, 10,378 were 60-69 years of age, 7,629 were 70-79 years of age, and 1,263 were 80 years of age or older. ZOSTAVAX® was demonstrated to be generally safe and effective in this population.

4.7 Effects on ability to drive and use machines
There are no data to suggest that ZOSTAVAX® affects the ability to drive or operate machinery.

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

ZOSTAVAX® Efficacy and Safety Trial (ZEST) in Subjects 50 to 59 Years of Age
In the ZEST study, subjects received a single dose of either ZOSTAVAX® (n=11,184) or placebo (n=11,212) and were monitored for general 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.

Vaccine-related injection-site and systemic adverse experiences reported at an incidence ≥1% are shown in Table 1. 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).

Table 1
Vaccine-Related Injection-Site and Systemic Adverse Experiences Reported in ≥1% of Adults Who Received ZOSTAVAX® or Placebo (1-42 Days Postvaccination) in the ZOSTAVAX® Efficacy and Safety Trial

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

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

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.

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

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

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

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

Vaccine-related injection-site and systemic adverse experiences reported at an incidence ≥1% are shown in Table 1. 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® versus subjects who received placebo (48% for ZOSTAVAX® and 17% for placebo).

Table 2
Vaccine-Related Injection-Site and Systemic Adverse Experiences Reported in ≥1% of Adults Who Received ZOSTAVAX® or Placebo (0-42 Days Postvaccination) in the Shingles Prevention Study

Adverse Experience	ZOSTAVAX (N = 3345) %	Placebo (N = 3271) %
Injection-Site		
Erythema[†]	35.6	6.9
Pain/tenderness[†]	34.3	8.6
Swelling[†]	26.1	4.5
Hematoma	1.6	1.4
Pruritus	7.1	1.0
Warmth	1.7	0.3

Systemic		
Headache	1.4	0.9

[†]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, 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 varicella-zoster virus (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.

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 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.

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

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

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

Immunogenicity in subjects 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 section 4.3 CONTRAINDICATIONS regarding corticosteroids.)

Immunogenicity in subjects with HIV infection

In a double-blind, placebo-controlled randomized clinical trial, ZOSTAVAX® was administered as a two-dose regimen to human immunodeficiency virus (HIV)-infected adults (18 years of age or older) on potent combination antiretroviral therapy with conserved immune function (CD4+ T cell count ≥ 200 cells/µL). Although a two-dose regimen was used in this study, ZOSTAVAX® is administered as a single dose regimen (See DOSAGE & ADMINISTRATION). In this clinical trial, a total of 295 subjects received dose 1 and 286 subjects received dose 2. All vaccinated study patients were followed for adverse experiences. Vaccine relatedness was determined by the investigator based upon blinded data. To evaluate the adverse experiences temporally associated with study vaccination, patients were given a Vaccination Report Card (VRC) to record any injection-site adverse experiences, systemic adverse experiences, elevated temperatures, and rashes through Week 6 following each vaccination. Patients were followed for serious adverse experiences, regardless of whether the event was related to the study vaccine, throughout the course of the study (through Week 24 following dose 1). In this clinical trial, the safety profile was generally similar to that seen in the Adverse Event Monitoring Substudy of the SPS. (See Section 4.3 CONTRAINDICATIONS regarding immunosuppression due to HIV/AIDS).

Post-marketing Experience

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

Gastrointestinal disorders: nausea
Infections and infestations: herpes zoster (vaccine strain)
Skin and subcutaneous tissue disorders: rash

Musculoskeletal and connective tissue disorders: arthralgia; myalgia
General disorders and administration site conditions: injection-site rash; injection-site urticaria; pyrexia; transient injection-site lymphadenopathy
Immune system disorders: hypersensitivity reactions including anaphylactic reactions

4.9 Overdose

There are no data with regard to overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Viral Vaccine
ATC code: J07BK02

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).

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-γ 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 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%). The observed vaccine efficacy in the LTPS is generally consistent with the vaccine efficacy for HZ observed during the SPS 70-year-old age group, and is consistent with the current age of the study cohort.

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 section 4.3 CONTRAINDICATIONS regarding corticosteroids).

Immunogenicity in subjects with HIV infection

In a double-blind, placebo-controlled randomized clinical trial, ZOSTAVAX® was administered as a two-dose regimen to human immunodeficiency virus (HIV)-infected adults (18 years of age or older) on potent combination antiretroviral therapy with conserved immune function (CD4+ T cell count ≥ 200 cells/µL). Although a two-dose regimen was used in this study, ZOSTAVAX® is administered as a single dose regimen (see section 4.2 Posology and Method of 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 section 4.3 CONTRAINDICATIONS regarding immunosuppression due to HIV/AIDS).

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.

5.2 Pharmacokinetic properties
Not applicable.

5.3 Preclinical safety data
Traditional non-clinical studies were not performed, but there are no non-clinical concerns considered relevant to clinical safety beyond data included in other sections of the Summary of Product Characteristics (SmPC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Powder:
Sucrose
Hydrolysed gelatin
Sodium chloride
Potassium dihydrogen phosphate
Potassium chloride
Monosodium L-glutamate monohydrate
Disodium phosphate
Sodium hydroxide (to adjust pH)
Urea

Solvent:
Water for injections

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
18 Months

6.4 Special precautions for 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.

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

DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.
DO NOT FREEZE THE RECONSTITUTED VACCINE.

6.5 Nature and contents of container

Powder in a vial (glass) with a stopper (butyl rubber) and flip off cap (aluminium) and solvent in a pre-filled syringe (glass) with plunger stopper (chlorobutyl rubber) and tip cap (styrene-butadiene rubber) with one or two unattached needles in a pack size of 1, 10 or 20.

Or

Powder in a vial (glass) with a stopper (butyl rubber) and flip off cap (aluminium) and solvent in a pre-filled syringe (glass) with plunger stopper (chlorobutyl rubber) and tip cap (styrene-butadiene rubber) without needle in pack size of 1, 10 or 20.

Or

Powder in a vial (glass) with a stopper (butyl rubber) and flip off cap (aluminium) and solvent in a pre-filled syringe (glass) with plunger stopper (chlorobutyl rubber) and needle shield (natural rubber), in a pack size of 1 or 10.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION/ PREQUALIFICATION HOLDER

MSD Pharmaceuticals Pvt. Ltd.,
Gala No. 1B, Building No. B-3,
City Link Warehouses Complex,
Mumbai Nashik Highway, Vadapa, Bhiwandi,
Thane 421302, Maharashtra, INDIA

8. MARKETING>AUTHORISATION NUMBER(S)

Import Permission No.: Import-63/2015

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorization (Form 45): 05 March 2015

Manufactured and packed by	**Imported and Marketed by**
Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN, Haarlem The Netherlands	MSD Pharmaceuticals Pvt. Ltd., Gala No. 1B, Building No. B-3, City Link Warehouses Complex, Mumbai Nashik Highway, Vadapa, Bhiwandi, Thane 421302, Maharashtra, INDIA

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