AUSTRALIAN PRODUCT INFORMATION
ZOSTAVAX® Zoster Virus Vaccine Live Refrigerator stable (Live varicella vaccine)

WARNINGS

Rarely, disseminated varicella zoster virus (VZV) infection with vaccine (Oka) strain can occur in patients following administration of the live-attenuated ZOSTAVAX vaccine. There have been fatal reports of disseminated vaccine-related VZV infection in Australia, including in patients on low dose immunosuppressive medication. The risk increases with the degree of immunosuppression.

ZOSTAVAX is contraindicated in patients with current or recent severe immunocompromising conditions from either a primary or acquired medical condition or medical treatment (See 4.3 CONTRAINDICATIONS).

Careful pre-screening and a risk-based assessment is required prior to administration of any dose of ZOSTAVAX. If appropriate, this assessment should include medical specialist consultation and potentially screening for pre-existing antibody to VZV. In such cases, vaccination should be deferred until such advice and/or results have been obtained.

The Australian Immunisation Handbook contains specific guidance about ZOSTAVAX administration in patients who are immunocompromised or have medical conditions that place them at risk of immunocompromise. If uncertain about a person's level of immunocompromise and whether vaccination is safe, **do not vaccinate** and seek further specialist advice.

Any patient who experiences a disseminated vesicular (chickenpox-like) rash 2 to 4 weeks after vaccine administration, or who feels unwell or has a fever, should seek medical attention immediately and ensure that their treating health professional is aware of their recent vaccination history.

If inadvertent vaccination in an immunosuppressed patient has occurred, the patient should be advised regarding the potential for disseminated VZV infection and the need to seek medical advice should symptoms suggestive of this occur, so that they can be considered for pre-emptive antiviral therapy.

If a recent ZOSTAVAX recipient is suspected of having disseminated VZV infection, the healthcare professional should:

- conduct appropriate diagnostic testing early in consultation with a clinical microbiologist or infectious diseases physician; and
- where appropriate, initiate appropriate empiric antiviral therapy whilst awaiting test results; and
- where feasible, cease immunosuppression in consultation with their treating specialist.

1 NAME OF THE MEDICINE

Live varicella vaccine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.65-mL dose contains a minimum of 19,400 PFU (plaque-forming units) of Oka/Merck strain of varicella-zoster virus (VZV) when reconstituted and stored at room temperature for up to 30 minutes.

List of excipients with known effect: sulfites (present as a residue of hydrolyzed porcine gelatin).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

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). During initial passage of the virus, tissue culture materials sourced from human embryonic stem cells may have been used in the research undertaken in the development of the vaccine. Further passage of the virus was performed at MSD 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.

3 PHARMACEUTICAL FORM

Powder for injection.

Powder and solvent for injection.

The powder is a white compact, crystalline pellet.

The solvent is a clear, colourless solution.

ZOSTAVAX, when reconstituted as directed, is a sterile preparation that is a semi-hazy to translucent, off white to pale yellow liquid for subcutaneous administration.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZOSTAVAX is indicated for the prevention of herpes zoster (shingles) in individuals 50 years of age and older.

ZOSTAVAX is indicated for the prevention of postherpetic neuralgia (PHN) and for reduction of acute and chronic zoster-associated pain in individuals 60 years of age and older.

4.2 DOSE AND METHOD OF ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION.

Do not inject intravascularly.

Individuals 50 years of age and older should receive a single dose (0.65mL) of the vaccine.

ZOSTAVAX is not a treatment for zoster or PHN.

Reconstitute immediately upon removal from the refrigerator.

PRODUCT IS FOR SINGLE USE IN ONE PATIENT ONLY.

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.

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

4.3 CONTRAINDICATIONS

ZOSTAVAX is contraindicated in any patients with the following:

- 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 5.1 CLINICAL TRIALS and 4.8 ADVERSE EFFECTS); cellular immune deficiencies.
- In patients with current or recent severe immunocompromising conditions from either a primary or acquired medical condition or medical treatment.
- Rarely, disseminated varicella zoster virus (VZV) infection with vaccine (Oka) strain can occur in patients following administration of the live-attenuated ZOSTAVAX vaccine. There have been fatal reports of disseminated vaccine-related VZV infection in Australia, including in patients on low dose immunosuppressive medication. The risk increases with the degree of immunosuppression.
- Active untreated tuberculosis.
- Pregnancy (see 4.6 Use in 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 4.3 CONTRAINDICATIONS).

As with any vaccine, adequate treatment provisions, including adrenaline (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 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 5.1 CLINICAL TRIALS and 4.8 ADVERSE 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 without a VZV-like rash has been reported but has not been confirmed. 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.

Use in the elderly
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. The safety and efficacy data presented in the sections 5 PHARMACOLOGICAL PROPERTIES, 5.1 CLINICAL TRIALS and 4.8 ADVERSE EFFECTS sections were obtained from these subjects. ZOSTAVAX was demonstrated to be generally safe and effective in this population.

Paediatric use
ZOSTAVAX is not recommended for use in this age group.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 concurrently with inactivated influenza vaccine (see 4.2 DOSE & METHOD OFADMINISTRATION and 5.1 CLINICAL TRIALS).

ZOSTAVAX and PNEUMOVAX 23 should not be given concomitantly because concomitant use resulted in reduced immunogenicity of ZOSTAVAX (see 5.1 CLINICAL TRIALS). Consider administration of the two vaccines separated by at least 4 weeks.

No data are currently available regarding the concomitant use of ZOSTAVAX with vaccines other than inactivated influenza vaccine and PNEUMOVAX 23.

Immunocompromise

The use of ZOSTAVAX has not been studied in subjects suffering any form of severe immunocompromise.

Revaccination

The duration of protection beyond 4 years after vaccination with ZOSTAVAX is unknown. The need for revaccination has not been defined.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no data on the potential of ZOSTAVAX to impair fertility.

Use in pregnancy
(Category B2)
Pregnancy Category B2: 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 4.3 CONTRAINDICATIONS).

Use in lactation
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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Studies
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.

<u>ZOSTAVAX Efficacy and Safety Trial (ZEST) in Subjects 50 to 59 Years of Age</u>
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: haematoma, 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, non-injection-site zoster-like 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 the frozen formulation of 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 vaccine-related injection-site and systemic adverse experiences were reported at an incidence ≥1% in the Adverse Event Monitoring Substudy. Most of these adverse experiences were reported as mild in intensity. Several adverse reactions were solicited (Days 0-4 postvaccination) and are designated with the * symbol.

[Very Common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1000, <1/100); Rare (≥1/10,000, <1/1,000); Very rare (<1/10,000) including isolated cases]

Nervous system disorder
Common: headache

General disorders and administration site conditions
Very common: erythema*, pain/tenderness*, swelling*
Common: haematoma, 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 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 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 zoster-like and varicella-like rashes within 42 days postvaccination were also low in both zoster vaccine recipients and placebo recipients. Of the 17 reported varicella-like and noninjection-site zoster-like rashes, 10 specimens were available and adequate for PCR testing. The Oka/Merck strain was identified by PCR analysis from the lesion specimens of only two subjects who reported varicella-like rashes (onset on Day 8 and 17).

A clinical trial (N= 695) was specifically designed to examine the safety and tolerability of a vaccine lot formulated at the maximal release potency. In the 461 subjects who received the maximal release potency, the adverse experience profile was as follows:

Nervous system disorder
Common: headache

General disorders and administration site conditions
Very common: erythema*, pain/tenderness*, pruritus, swelling*
Common: fatigue, haematoma, warmth

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 as well as vaccine-related systemic adverse experiences were reported among subjects 50-59 years of age compared with subjects ≥60 years of age. The most frequently reported vaccine-related systemic adverse experience was headache (1% in both groups).

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.

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 20mg of prednisone for at least 2 weeks prior to enrolment, 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 4.3 CONTRAINDICATIONS regarding corticosteroids).

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

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.

The clinical safety of refrigerator-stable ZOSTAVAX (n=182) was compared with that of a frozen formulation of ZOSTAVAX (n=187) for 28 days postvaccination. The safety profiles were comparable for the two different formulations and were similar to those seen in the AE Monitoring Substudy of the SPS. At Week 4, the overall incidence of vaccine-related injection-site adverse experiences was 36% for the refrigerator-stable formulation vs. 46% for the frozen formulation of ZOSTAVAX. The overall incidence of vaccine-related systemic adverse experiences was 6% for both groups.

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.

Infections and infestations: varicella (vaccine strain), herpes zoster (vaccine strain)

Gastrointestinal disorders: nausea

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

Skin and subcutaneous tissue disorders: rash

Eye Disorders: Necrotizing retinitis (patients on immunosuppressive therapy)

Nervous system disorders: Guillain-Barré syndrome; facial paralysis

There have been fatal cases of disseminated disease in immunocompromised patients.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There are no data with regard to overdose.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Epidemiology

Herpes Zoster

Herpes zoster (HZ), commonly known as shingles or simply "zoster," is a manifestation of the reactivation of VZV, which, as a primary infection, produces chickenpox (varicella). Following initial infection, the virus remains latent in the dorsal root or cranial sensory ganglia until it reactivates, producing zoster. 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. 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. 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.

Zoster may be associated with serious complications, such as postherpetic neuralgia (PHN) and scarring; less commonly, bacterial superinfection and motor neuron palsies; and rarely 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 debilitating diseases such 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. 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.

5.1 PHARMACODYNAMIC PROPERTIES

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 5.1 CLINICAL TRIALS: *Immunogenicity*).

Clinical trials

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, 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). Subjects 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%]). The effect of ZOSTAVAX on post-herpetic neuralgia was not evaluated in the ZEST trial.

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

In the Shingles Prevention Study (SPS)[1], a placebo-controlled, double-blind clinical trial of the frozen formulation 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. The racial distribution was as follows for the ZOSTAVAX and placebo groups: white (95%); black (2.0%); Hispanic-American (1.0%); and other (1.0%). The gender distribution was 59% male and 41 % female in both vaccination groups. The age range of subjects enrolled was 59-99.

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 offered 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)[2], 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 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 Table 1).

[1] Oxman MN, Levin MJ, Johnson GR, *et al*.. A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults. NEJM 2005;352:2271-84.

[2] Coplan PM, Schmader K, Nikas A, *et al*. Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: Adaptation of the brief pain inventory. J Pain 2004;5(6):344-56

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

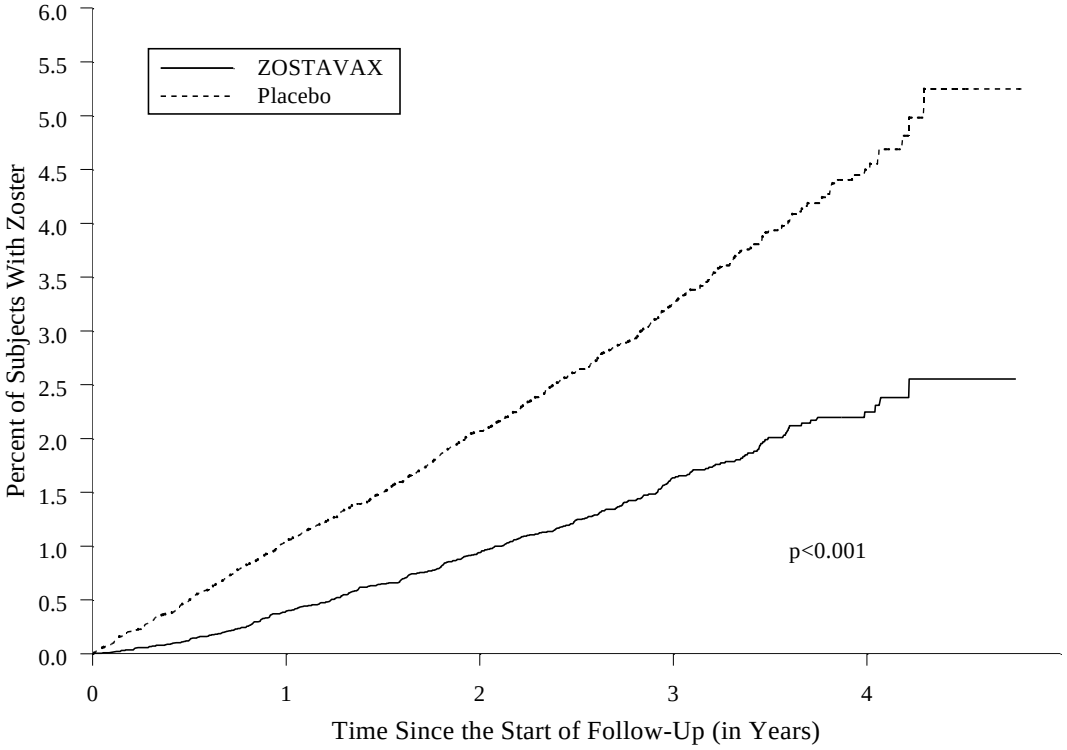
Endpoint	Vaccine efficacy	95% CI
Incidence of Zoster		
Overall	51%	44 to 58%
60-69 years	64%	56 to 71%
≥ 70 years	38%	25 to 48%
Incidence of PHN**		
Overall	67%	48 to 79%
60-69 years	66%	20 to 87%
≥ 70 years	67%	43 to 81%
HZ Pain BOI†**		
Overall	61%	51 to 69%
60-69 years	66%	52 to 76%
≥ 70 years	55%	40 to 67%

* Study was conducted using the frozen formulation of ZOSTAVAX
**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 cases [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 ($p<0.001$; Figure 1).

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

Prevention Study



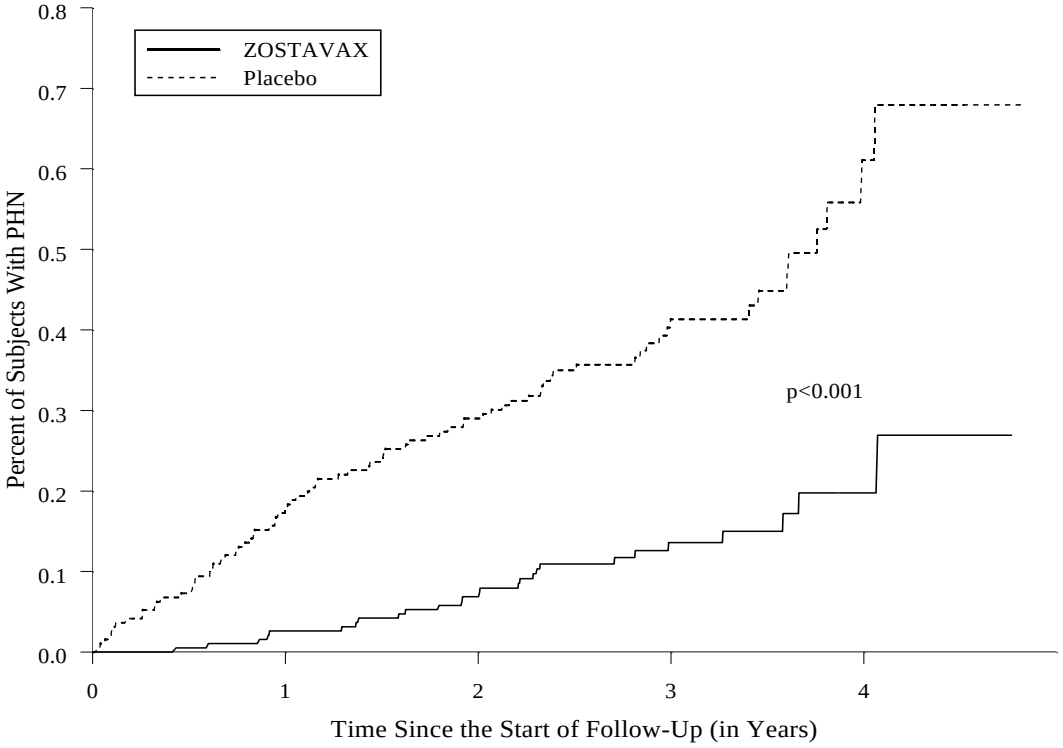
*A limited number of subjects were followed beyond Year 4.

ZOSTAVAX 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 in the overall study population was 67% (95% CI: [48 to 79%]), and the reduction was similar for the two age groups (60-69 and ≥70 years of age). Among subjects 60 to 69 years of age, the benefit of ZOSTAVAX in the prevention of PHN can be primarily attributed to the effect of the vaccine on the prevention of zoster (64% efficacy against zoster, 66% efficacy against PHN, Table 1). In subjects ≥70 years of age, the prevention of PHN was achieved through a combination of the prevention of zoster and a reduction in the severity and duration of zoster-associated pain, and thus PHN, (38% efficacy against zoster and 67% efficacy against PHN, Table 1).

For the subset of subjects who developed zoster despite vaccination, an additional benefit in reduction of PHN was seen only in subjects 70 years of age and older.

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 ($p<0.001$; Figure 2).

Figure 2
Kaplan-Meier Plot of the Cumulative Incidence of PHN Over Time* in the Shingles Prevention Study



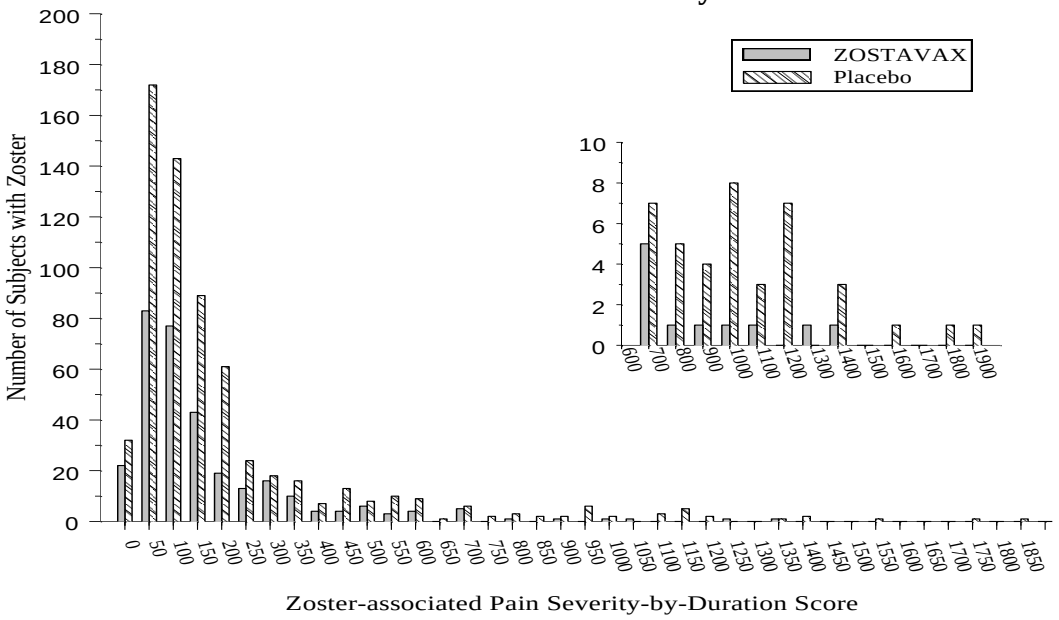
*A limited number of subjects were followed beyond Year 4.

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 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 had severity-by-duration scores >600, compared with 40 subjects who received placebo. (See Figure 3.)

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).

Figure 3
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 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 reduction (8%) 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. This reduction was not statistically significant. 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.

Fewer complications were reported by subjects who received ZOSTAVAX 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 2.

Table 2
Number of Subjects with Specific Complications* of Zoster that were Reported in the Shingles Prevention Study

Complication	ZOSTAVAX (N = 19,270; n = 321)	Placebo (N = 19,276; n = 659)
Allodynia	135	310
Bacterial Superinfection	3	7
Dissemination	5	11
Impaired Vision**	2	9
Peripheral Nerve Palsies (motor)	5	12
Ptosis**	2	9
Scarring	24	57
Sensory Loss	7	12

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 ≥1% in at least one vaccination group among subjects with zoster.
**Ophthalmic zoster occurred in 35 subjects vaccinated with ZOSTAVAX vs. 69 subjects who received placebo.

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

ZOSTAVAX Efficacy and Safety Trial (ZEST) in Subjects aged 50-59 years
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 titre [GMT] of 664 vs. 288 gpELISA units/mL, $p<0.001$).

Shingles Prevention Study (SPS) in Subjects 60 Years of Age and Older
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 titre [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/106 PBMCs], $p<0.001$) were demonstrated.

The VZV antibody (gpELISA) titres were at the highest level 6 weeks after administration of the zoster vaccine and then gradually decreased over 36 months to a level slightly above the prevaccination level. The zoster vaccine recipients maintained a higher fold-rise of IFN-γ ELISPOT counts compared with placebo recipients up to 36 months postvaccination. Other studies

The immunogenicity of a refrigerator-stable formulation of ZOSTAVAX was shown to be similar to that of a frozen formulation of ZOSTAVAX in a single bridging study. The study enrolled 368 subjects randomized in a 1:1 ratio to receive a dose of either the refrigerator-stable or frozen formulation of ZOSTAVAX. Subjects were stratified by age (50 to 59 years and ≥ 60 years) in a 1:2 ratio. Blood samples were collected at day 1 and week 4 postvaccination to assess VZV antibody responses. ZOSTAVAX refrigerator stable and frozen formulations elicited similar VZV antibody responses as measured by gpELISA (GMTs of 727 vs. 834 gpELISA units/mL, respectively at week 4).

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%). 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 with inactivated influenza vaccine

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 non-concomitantly (N=380) with inactivated influenza vaccine. Subjects enrolled in the concomitant group received ZOSTAVAX and influenza vaccine on Day 1 and placebo at Week 4. Subjects enrolled in the non-concomitant group received influenza vaccine and placebo on Day 1 and ZOSTAVAX at Week 4. The antibody responses at 4 weeks postvaccination to ZOSTAVAX were similar, whether administered concomitantly or non-concomitantly (GMT's of 554 vs. 597 gpELISA units/mL). The geometric mean fold-rise of immune response following vaccination was acceptable in the concomitant group as measured by gpELISA (2.1-fold (95% CI:[2.0 to 2.3]). Influenza antibody responses at 4 weeks post vaccination were similar and satisfactory, whether administered concomitantly or non-concomitantly.

In another double-blind, controlled study, 882 adults in the US, 50 years of age and older (median age = 60 years), were randomized to receive quadrivalent inactivated influenza vaccine and ZOSTAVAX concurrently (N=440), or quadrivalent inactivated influenza vaccine alone followed 4 weeks later by ZOSTAVAX alone (N=442). The antibody responses to both vaccines at 4 weeks postvaccination were similar in both groups.

Immunogenicity following concomitant administration with pneumococcal vaccine

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 non-concomitant 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 non-concomitant 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 non-concomitantly.

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 4.3 CONTRAINDICATIONS regarding corticosteroids). Immunogenicity of ZOSTAVAX in patients taking chronic / maintenance systemic corticosteroids has not been compared with subjects receiving ZOSTAVAX alone in the same study.

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 4.2 DOSE AND METHOD OF ADMINISTRATION). In this study, a total of 295 subjects received dose one and 286 subjects received dose two. Compared with placebo, ZOSTAVAX induced a higher VZV-specific gpELISA antibody GMT at Week 6 (6 weeks following dose one) and Week 12 (6 weeks following dose two) (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 4.3 CONTRAINDICATIONS regarding immunosuppression due to HIV/AIDS.)

5.2 PHARMACOKINETIC PROPERTIES

Not applicable.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
ZOSTAVAX has not been evaluated for genotoxicity.

Carcinogenicity
No animal carcinogenicity studies have been conducted with ZOSTAVAX.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

sucrose
hydrolysed gelatin* (porcine)
urea
sodium chloride
monosodium glutamate monohydrate
dibasic sodium phosphate
monobasic potassium phosphate
potassium chloride
residual components of MRC-5 cells including DNA and protein
trace quantities of neomycin, and bovine calf serum

*contains sulfites

Diluent
Water for injections

The product contains no preservatives.

The manufacture of this product includes exposure to bovine derived material. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

6.2 INCOMPATIBILITIES

Please refer to 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for further information.

6.3 SHELF LIFE

18 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

ZOSTAVAX SHOULD BE STORED REFRIGERATED at an average temperature of 2 to 8°C (36 to 46°F) until it is reconstituted for injection. 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).

DO NOT FREEZE THE RECONSTITUTED VACCINE.

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

Before reconstitution, protect from light.

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).

6.5 NATURE AND CONTENTS OF CONTAINER

ZOSTAVAX is supplied as follows:

(1) a single-dose (glass) vial of lyophilized vaccine, in packs of 1 or 10.
(2) a single-dose (glass) vial of lyophilized vaccine, in packs of 1 or 10, supplied with a separate package of 1 or 10 single dose (glass) vials of sterile diluent.
(3) a single-dose (glass) vial of lyophilized vaccine, in packs of 1 or 10, supplied with a separate package of 1 or 10 needleless (glass) syringes of sterile diluent
(4) a single-dose (glass) vial of lyophilized vaccine and single-dose (glass) vial of sterile diluent in composite packs of 1, 5 or 10.
(5) a single-dose (glass) vial of lyophilized vaccine and needleless (glass) syringe of sterile diluent in composite packs of 1 or 10

Not all presentations and pack sizes may be supplied.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure
Not applicable.

CAS number
Not applicable.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Medicine

8 SPONSOR

NAME AND ADDRESS OF SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road
Macquarie Park NSW 2113
http://www.msd-australia.com.au
Tel (+61) 02 8988 8000

NAME AND ADDRESS OF DISTRIBUTOR

Seqirus (Australia) Pty Ltd
Melbourne, Victoria
Australia
http://www.seqirus.com.au
Tel: 1800 642 865

9 DATE OF FIRST APPROVAL

13 January 2010

10 DATE OF REVISION

28 September 2022

Summary table of changes

Section changed	Summary of new information
6.1	Updated to reflect presence of sulfite in gelatin and to include information on diluent
6.5	Editorial update only
8	Updated Sponsor and distributor details

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