

1 PRODUCT NAME

ZOSTAVAX ®

Zoster Vaccine Live (Oka/Merck)

Refrigerator stable

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution with accompanying vial or pre-filled syringe of diluent, 1 dose (0.65 mL) contains a minimum of 19,400 PFU (plaque forming units) of the Oka/Merck strain of varicella-zoster virus (VZV).

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Injection with diluent

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 immunisation of individuals 50 years of age or older.

4.2 Dose and method of administration

For subcutaneous administration. Do not inject intravenously.

Individuals should receive a single dose.

ZOSTAVAX is not a treatment for zoster or PHN.

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

Reconstitute immediately upon removal from the refrigerator.

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

Vial of diluent:

To reconstitute the vaccine, first withdraw the entire contents of the diluent vial into a syringe. Inject all of the diluent in the syringe into the vial of lyophilised 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 MINIMISE 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 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 vaccine products should be inspected visually for particulate matter and discolouration 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 leukaemias; lymphoma; other conditions affecting the bone marrow or lymphatic system; immunosuppression due to HIV/AIDS (see Sections 4.8 and 5.1); cellular immune deficiencies.

Immunosuppressive therapy (including high-dose corticosteroids), See Section 4.8; 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.

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

Active untreated tuberculosis.

Pregnancy (see Section 4.6).

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).

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

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

The safety and efficacy of ZOSTAVAX have not been established in adults who are known to be infected with human immunodeficiency virus (HIV) with or without evidence of immunosuppression. A phase II safety and immunogenicity study in HIV-infected adults with conserved immune function has been completed (see Sections 4.8 and 5.1).

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.

Paediatric 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.

Animal Toxicology

Carcinogenesis, Mutagenesis, Reproduction

ZOSTAVAX has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility.

Revaccination

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

4.5 Interaction with other medicines 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 can be administered concomitantly with inactivated influenza vaccine using separate syringes (see Section 4.2).

ZOSTAVAX and PNEUMOVAX[®] 23 should not be given concomitantly because concomitant use resulted in reduced immunogenicity of ZOSTAVAX (see Section 5.1, Immunogenicity following concomitant administration). Consider administration of the two vaccines separated by at least 4 weeks.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal reproduction studies have not been conducted with ZOSTAVAX. It is also not known whether ZOSTAVAX can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. However, naturally-occurring VZV infection is known to sometimes cause foetal harm. Therefore, ZOSTAVAX should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination (see Section 4.3).

Breast-feeding 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.

Fertility

ZOSTAVAX has not been evaluated in fertility studies.

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 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 post-vaccination in addition to undergoing routine safety monitoring throughout the study.

The following very common ($\geq 1/10$) and common ($\geq 1/100$, $< 1/10$) vaccine-related injection-site and systemic adverse experiences were reported in the ZEST study. Several adverse experiences were solicited (Days 1-5 post-vaccination) 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 post-vaccination 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 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 Sub-study, 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 post-vaccination in addition to undergoing routine safety monitoring throughout the study.

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

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 Sub-study.

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

Within the same 42-day post-vaccination 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 non-injection-site zosteriform and varicella-like rashes within 42 days post-vaccination 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 Sub-study 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, randomised 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 Sub-study of the SPS.

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

In 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 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 Section 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/ μ L). Although a two-dose regimen was used in this study, ZOSTAVAX is administered as a single dose regimen (see Section 4.2). 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.

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

Gastrointestinal disorders: nausea

Skin and subcutaneous tissue disorders: rash

Musculoskeletal and connective tissue disorders: arthralgia; myalgia

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

Immune system disorders: hypersensitivity reactions including anaphylactic reactions

Eye Disorders: Necrotizing retinitis (patients on immunosuppressive therapy)

Nervous system disorders: Guillain-Barré syndrome; facial paralysis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions.

<https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

There is no data with regard to overdose. For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Herpes Zoster

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

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

Anyone who has been infected with VZV, including those without a clinical history of varicella, is at risk for developing zoster, which is considered to be due to waning immunity to VZV. Nearly all adults are at risk for zoster in Australia and New Zealand (24 million population in 2005), where an estimated 80,000 cases occur every year. This number is expected to rise with the aging of the population. The incidence and severity of zoster, as well as the frequency and severity of its complications, increase markedly with age, with two-thirds of the cases occurring in individuals older than 50 years of age. In recent studies, the lifetime risk of zoster has been estimated to be as high as 30% in the general population. It is estimated that by 85 years of age, 50% of individuals will have experienced an episode of zoster.

Zoster-associated hospitalisation rates vary across countries and are estimated to range from 5 to 10 per 100,000 population for an average length of stay of 10 to 13 days. The proportion of zoster patients hospitalised increases with age, up to more than 10% in individuals over 65 years of age. Seventy to 80% of hospitalisations for zoster occur among immunocompetent individuals. Available hospitalisation data for zoster are limited in Australia and New Zealand. Based on a recent Australian study, approximately 5,000 zoster-associated hospitalisations, including 2,000 in which the primary diagnosis is zoster, occur each year with an average length of stay of 13 days.

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

Zoster-associated pain and discomfort can be prolonged and disabling and can diminish

quality of life and functional capacity to a degree comparable to such debilitating diseases as congestive heart failure, myocardial infarction, type II diabetes mellitus, and major depression.

Postherpetic Neuralgia

Postherpetic neuralgia (PHN) constitutes the most common serious complication of HZ and cause of zoster-associated morbidity in the immunocompetent host. Based on extrapolation of published prevalence data, the prevalence of PHN is estimated to be 40,000 to 80,000 cases in Australia and New Zealand (24 million population). The frequency and severity of PHN increase with age, and may complicate 25 to 50% of zoster cases among patients over 50 years of age. PHN has been described as tender, burning, throbbing, stabbing, shooting and/or sharp pain that can persist for months or even years and can also lead to emotional distress. Allodynia (pain from an innocuous stimulus) is present in at least 90% of patients with PHN and is typically described as the most distressing and debilitating types of pain. Several definitions of PHN are widely used in the medical community, including pain persisting longer than 90 days after the onset of the rash.

Mechanism of Action

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

Clinical efficacy and safety

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 randomised 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 randomised 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). Randomisation 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 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 60-69 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). 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).

For the subjects who developed zoster despite vaccination, an additional benefit in the reduction in PHN was seen only in subjects 70 years of age and older. In addition, the efficacy of ZOSTAVAX did not change appreciably when PHN was defined using alternative cut-off 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 favourable, 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 medicines 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.

Long-Term Effectiveness Study in Individuals 50 Years of Age or Older

An interim analysis from a large ongoing US prospective observational cohort study of the long-term effectiveness of ZOSTAVAX in individuals 50 years of age or older at the time of vaccination has shown that ZOSTAVAX is effective in reducing HZ and PHN incidence in vaccinated individuals as compared to an unvaccinated reference group.

During the 2007 to 2014 study period, out of 1,355,720 study individuals, 392,677 received ZOSTAVAX. A total of 48,889 confirmed HZ cases and 3,316 confirmed PHN cases (>90 days of zoster-associated pain) were observed.

Vaccine effectiveness (VE) against HZ was evaluated for up to eight years postvaccination. VE estimates by age at vaccination and average VE estimates over the first 3 and 5 years postvaccination are shown below (see Table 2).

Table 2: VE* of ZOSTAVAX against HZ over the Study Period and on Average over 3 and 5 years, by Age at Vaccination. 2007 to 2014

	Age at vaccination [†]				
	50-59 years	60-69 years	70-79 years	80+ years	Among all age groups
	VE % (95% CI)	VE % (95% CI)	VE % (95% CI)	VE % (95% CI)	VE % (95% CI)
VE over study period[‡]					
2007-2014	60% (53, 65)	51% (48, 53)	46% (43, 49)	47% (43, 52)	49% (48, 51)
Average VE[§]					
3-year postvaccination	60% (52, 66)	55% (52, 57)	50% (47, 53)	48% (43, 53)	52% (51, 54)
5-year postvaccination	¶	49% (47, 52)	46% (43, 48)	44% (38, 49)	47% (46, 49)

* VE was estimated for the first episode of herpes zoster during follow-up and was calculated as (1-hazards ratio)*100

† Cox models adjusted for calendar time, age, sex, race/ethnic group, healthcare resource utilization (flu vaccination, number of weeks with an outpatient visit per year), co-morbid conditions (DxCG score, HCUP risk score), immunocompromise status during follow-up

‡ VE over study period is the VE calculated over the full duration of the study (2007-2014) at the time of this interim analysis

§ Average VE was calculated as the weighted average of the annual VE estimates over 3 and 5 years, respectively, where the weights are the proportion of the overall time period covered

¶ Data not available at the time of this interim analysis

Abbreviations: VE denotes vaccine effectiveness; CI confidence interval; DxCG diagnostic cost group; HCUP healthcare cost and utilization project

Similarly, VE against PHN was evaluated for up to eight years postvaccination. VE estimates by age at vaccination and average VE estimates over the first 3 and 5 years postvaccination are shown below (see Table 3).

Table 3: VE* of ZOSTAVAX against Postherpetic Neuralgia (PHN) over the Study Period and on Average over 3 and 5 years, by Age at Vaccination. 2007 to 2014

	Age at vaccination [†]				
	50-59 years	60-69 years	70-79 years	80+ years	Among all age groups
	VE % (95% CI)	VE % (95% CI)	VE % (95% CI)	VE % (95% CI)	VE % (95% CI)
VE over study period[‡]					
2007-2014	63% (11, 85)	71% (65, 76)	70% (63, 75)	62% (50, 71)	69% (65, 72)
Average VE[§]					
3-year postvaccination	¶	74% (66, 80)	73% (65, 79)	63% (49, 73)	71% (66, 75)
5-year postvaccination	¶	72% (65, 77)	69% (62, 75)	61% (47, 71)	68% (64, 72)

* VE was estimated for the first episode of herpes zoster during follow-up and was calculated as (1-hazards ratio)*100

† Cox models adjusted for calendar time, age, sex, race/ethnic group, healthcare resource utilization (flu vaccination, number of weeks with an outpatient visit per year), co-morbid conditions (DxCG score, HCUP risk score), immunocompromise status during follow-up

‡ VE over study period is the VE calculated over the full duration of the study (2007-2014) at the time of this interim analysis

§ Average VE was calculated as the weighted average of the annual VE estimates over 3 and 5 years, respectively, where the weights are the proportion of the overall time period covered

¶ Data not available at the time of this interim analysis

Abbreviations: VE denotes vaccine effectiveness; CI confidence interval; DxCG diagnostic cost group; HCUP healthcare cost and utilization project

Immunogenicity of ZOSTAVAX

Within the ZOSTAVAX Efficacy and Safety Trial (ZEST), immune responses to vaccination were evaluated in a random 10% sub-cohort (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 post-vaccination 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, $p < 0.001$).

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 post-vaccination 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.

In an integrated analysis of two clinical trials evaluating immune response to ZOSTAVAX at 4 weeks post-vaccination, 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

In a double-blind, controlled clinical trial, 762 adults 50 years of age and older were randomised 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 to both vaccines at 4 weeks post-vaccination 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.

In a double-blind, controlled clinical trial, 473 adults, 60 years of age or older, were randomised 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 post-vaccination, 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 post-vaccination 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, randomised 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 post-vaccination, 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 \geq 200 cells/ μ L). Although a two-dose regimen was used in this study, ZOSTAVAX is administered as a single dose regimen (see Section 4.2). 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.)

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 Data Sheet.

6 PHARMACEUTICAL PARTICULARS

Chemistry

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

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.

6.1 List of excipients

Powder:

Sucrose

Hydrolysed porcine gelatin

Urea

Sodium chloride

Monosodium L glutamate

Sodium phosphate dibasic

Potassium phosphate monobasic

Potassium chloride

Residual components of MRC-5 cells including DNA and protein

Trace quantities of neomycin and bovine calf serum

The product contains no preservative.

Solvent:

Water for injection

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.

IT IS RECOMMENDED THAT THE VACCINE BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION, TO MINIMISE LOSS OF POTENCY.

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

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, but not to exceed temperatures lower than -50°C (-58°F). Use of dry ice may subject ZOSTAVAX to temperatures colder than -50°C (-58°F).

ZOSTAVAX SHOULD BE STORED REFRIGERATED at a temperature of 2-8°C (36 to 46°F) or colder until it is reconstituted for injection (see Section 4.2). 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.

DO NOT FREEZE THE RECONSTITUTED VACCINE.

6.5 Nature and contents of container

ZOSTAVAX is supplied as follows:

- Vial of vaccine and vial of diluent in packs of 1* or 10*
- Vial of vaccine and pre-filled diluent syringe in packs of 1 or 10

**currently not available in New Zealand*

6.6 Special precautions for disposal

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Merck Sharp & Dohme (New Zealand) Limited
P O Box 99 851
Newmarket
Auckland
NEW ZEALAND

9 DATE OF FIRST APPROVAL

11 September 2008

10 DATE OF REVISION OF THE TEXT

16 August 2018

S-WPC-V211-R-I-052018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8 Undesirable effects	Update to Post marketing experience section for addition of Nervous system disorders.