

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZOSTAVAX safely and effectively. See full prescribing information for ZOSTAVAX.

ZOSTAVAX® (Zoster Vaccine Live)
Suspension for subcutaneous injection
Initial U.S. Approval: 2006

RECENT MAJOR CHANGES

Contraindications, Immunosuppression (4.2) -----03/2018

INDICATIONS AND USAGE

ZOSTAVAX is a live attenuated virus vaccine indicated for prevention of herpes zoster (shingles) in individuals 50 years of age and older. (1)

Limitations of Use of ZOSTAVAX:

- ZOSTAVAX is not indicated for the treatment of zoster or postherpetic neuralgia (PHN) (1)
- ZOSTAVAX is not indicated for prevention of primary varicella infection (Chickenpox) (1)

DOSAGE AND ADMINISTRATION

Single 0.65 mL subcutaneous injection (2.1)

DOSAGE FORMS AND STRENGTHS

Single dose vials with not less than 19,400 plaque-forming units [PFU] per 0.65 mL dose when reconstituted to a suspension. (2.1, 3, 16)

CONTRAINDICATIONS

- History of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine. (4.1)
- Immunosuppression or Immunodeficiency. (4.2)
- Pregnancy. (4.3, 8.1)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions including anaphylaxis have occurred with ZOSTAVAX (5.1)
- Transmission of vaccine virus may occur between vaccinees and susceptible contacts (5.2)
- Deferral should be considered in acute illness (for example, in the presence of fever) or in patients with active untreated tuberculosis (5.3)
- Avoid pregnancy for 3 months following vaccination with ZOSTAVAX (8.1)

ADVERSE REACTIONS

The most frequent adverse reactions, reported in $\geq 1\%$ of subjects vaccinated with ZOSTAVAX, were headache and injection-site reactions. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

DRUG INTERACTIONS

In a randomized clinical study, a reduced immune response to ZOSTAVAX as measured by gpELISA was observed in individuals who received concurrent administration of PNEUMOVAX® 23 and ZOSTAVAX compared with individuals who received these vaccines 4 weeks apart. Consider administration of the two vaccines separated by at least 4 weeks. (7.1, 14.4)

USE IN SPECIFIC POPULATIONS

Pregnancy: Do not administer ZOSTAVAX to females who are pregnant. Pregnancy should be avoided for 3 months following vaccination with ZOSTAVAX. (4.3, 8.1, 17)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 01/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose and Schedule

2.2 Preparation for Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

4.1 Hypersensitivity

4.2 Immunosuppression

4.3 Pregnancy

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

5.2 Transmission of Vaccine Virus

5.3 Concurrent Illness

5.4 Limitations of Vaccine Effectiveness

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 VZV Rashes Following Vaccination

6.3 Post-Marketing Experience

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

7.2 Antiviral Medications

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

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

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

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

14.4 Concomitant Use Studies

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZOSTAVAX® is a live attenuated virus vaccine indicated for prevention of herpes zoster (shingles) in individuals 50 years of age and older.

Limitations of Use of ZOSTAVAX:

- ZOSTAVAX is not indicated for the treatment of zoster or postherpetic neuralgia (PHN).

- ZOSTAVAX is not indicated for prevention of primary varicella infection (Chickenpox).

2 DOSAGE AND ADMINISTRATION

Subcutaneous administration only. Do not inject intravascularly or intramuscularly.

2.1 Recommended Dose and Schedule

Administer ZOSTAVAX as a single 0.65-mL dose subcutaneously in the deltoid region of the upper arm.

2.2 Preparation for Administration

Use only sterile syringes free of preservatives, antiseptics, and detergents for each injection and/or reconstitution of ZOSTAVAX. Preservatives, antiseptics and detergents may inactivate the vaccine virus.

ZOSTAVAX is stored frozen and should be reconstituted immediately upon removal from the freezer.

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

Reconstitution:

- Use only the diluent supplied.
- Withdraw the entire contents of the diluent into a syringe.
- To avoid excessive foaming, slowly inject all of the diluent in the syringe into the vial of lyophilized vaccine and gently agitate to mix thoroughly.
- Withdraw the entire contents of reconstituted vaccine into a syringe and inject the total volume subcutaneously.
- **ADMINISTER IMMEDIATELY AFTER RECONSTITUTION** to minimize loss of potency. Discard reconstituted vaccine if not used within 30 minutes. Do not freeze reconstituted vaccine.

3 DOSAGE FORMS AND STRENGTHS

ZOSTAVAX is a lyophilized preparation of live, attenuated varicella-zoster virus (Oka/Merck) to be reconstituted with sterile diluent to give a single dose suspension with a minimum of 19,400 PFU (plaque forming units) when stored at room temperature for up to 30 minutes.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer ZOSTAVAX to individuals with a history of anaphylactic/anaphylactoid reaction to gelatin, neomycin or any other component of the vaccine. Neomycin allergy manifested as contact dermatitis is not a contraindication to receiving this vaccine. {1}

4.2 Immunosuppression

Do not administer ZOSTAVAX to individuals who are immunodeficient or immunosuppressed due to disease or therapy, as serious or fatal disseminated vaccine strain varicella-zoster virus disease may occur. Causes of immunodeficiency or immunosuppression may include, but are not limited to, primary or acquired immunodeficiency states, AIDS or other clinical manifestations of infection with human immunodeficiency viruses, leukemia, lymphoma or other malignant neoplasms affecting the bone marrow or lymphatic system, and immunosuppressive therapy.

4.3 Pregnancy

Do not administer ZOSTAVAX to pregnant women. Naturally occurring varicella-zoster virus (VZV) infection is known to sometimes cause fetal harm. Pregnancy should be avoided for 3 months following administration of ZOSTAVAX [see *Use in Specific Populations (8.1) and Patient Counseling Information (17)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious adverse reactions, including anaphylaxis, have occurred with ZOSTAVAX. Adequate treatment provisions, including epinephrine injection (1:1,000), should be available for immediate use should an anaphylactic/anaphylactoid reaction occur.

5.2 Transmission of Vaccine Virus

Transmission of vaccine virus may occur between vaccinees and susceptible contacts.

5.3 Concurrent Illness

Deferral should be considered in acute illness (for example, in the presence of fever) or in patients with active untreated tuberculosis.

5.4 Limitations of Vaccine Effectiveness

Vaccination with ZOSTAVAX does not result in protection of all vaccine recipients.

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

6 ADVERSE REACTIONS

The most frequent adverse reactions, reported in $\geq 1\%$ of subjects vaccinated with ZOSTAVAX, were headache and injection-site reactions.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, rates of adverse reactions observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

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). The racial distribution across both vaccination groups was similar: White (94.4%); Black (4.2%); Hispanic (3.3%) and Other (1.4%) in both vaccination groups. The gender distribution was 38% male and 62% female in both vaccination groups. The age distribution of subjects enrolled, 50 to 59 years, was similar in both vaccination groups. All subjects received a vaccination report card (VRC) to record adverse events occurring from Days 1 to 42 postvaccination.

In the ZEST study, serious adverse events occurred at a similar rate in subjects vaccinated with ZOSTAVAX (0.6%) or placebo (0.5%) from Days 1 to 42 postvaccination.

In the ZEST study, all subjects were monitored for adverse reactions. An anaphylactic reaction was reported for one subject vaccinated with ZOSTAVAX.

Most Common Adverse Reactions and Experiences in the ZEST Study

The overall incidence of vaccine-related injection-site adverse reactions within 5 days postvaccination was greater for subjects vaccinated with ZOSTAVAX as compared to subjects who received placebo (63.6% for ZOSTAVAX and 14.0% for placebo). Injection-site adverse reactions occurring at an incidence $\geq 1\%$ within 5 days postvaccination are shown in Table 1.

Table 1: Injection-Site Adverse Reactions Reported in $\geq 1\%$ of Adults Who Received ZOSTAVAX or Placebo Within 5 Days Postvaccination in the ZOSTAVAX Efficacy and Safety Trial

Injection-Site Adverse Reaction	ZOSTAVAX (N = 11094) %	Placebo (N = 11116) %
<i>Solicited*</i>		
Pain	53.9	9.0
Erythema	48.1	4.3
Swelling	40.4	2.8
<i>Unsolicited</i>		
Pruritus	11.3	0.7
Warmth	3.7	0.2
Hematoma	1.6	1.6
Induration	1.1	0.0

*Solicited on the Vaccination Report Card

Systemic adverse reactions and experiences reported during Days 1-42 at an incidence of $\geq 1\%$ in either vaccination group were headache (ZOSTAVAX 9.4%, placebo 8.2%) and pain in the extremity (ZOSTAVAX 1.3%, placebo 0.8%), respectively.

The overall incidence of systemic adverse experiences reported during Days 1-42 was higher for ZOSTAVAX (35.4%) than for placebo (33.5%).

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

In the SPS, the largest clinical trial of ZOSTAVAX, subjects received a single dose of either ZOSTAVAX (n=19,270) or placebo (n=19,276). The racial distribution across both vaccination groups was similar: White (95%); Black (2.0%); Hispanic (1.0%) and Other (1.0%) in both vaccination groups. The gender distribution was 59% male and 41% female in both vaccination groups. The age distribution of subjects enrolled, 59-99 years, was similar in both vaccination groups.

The Adverse Event Monitoring Substudy of the SPS, designed to provide detailed data on the safety profile of the zoster vaccine (n=3,345 received ZOSTAVAX and n=3,271 received placebo) used vaccination report cards (VRC) to record adverse events occurring from Days 0 to 42 postvaccination (97% of subjects completed VRC in both vaccination groups). In addition, monthly surveillance for hospitalization was conducted through the end of the study, 2 to 5 years postvaccination.

The remainder of subjects in the SPS (n=15,925 received ZOSTAVAX and n=16,005 received placebo) were actively followed for safety outcomes through Day 42 postvaccination and passively followed for safety after Day 42.

Serious Adverse Events Occurring 0-42 Days Postvaccination

In the overall SPS study population, serious adverse events occurred at a similar rate (1.4%) in subjects vaccinated with ZOSTAVAX or placebo.

In the AE Monitoring Substudy, the rate of SAEs was increased in the group of subjects who received ZOSTAVAX as compared to the group of subjects who received placebo (Table 2).

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

Cohort	ZOSTAVAX n/N %	Placebo n/N %	Relative Risk (95% CI)
Overall Study Cohort	255/18671	254/18717	1.01
(60 years of age and older)	1.4%	1.4%	(0.85, 1.20)
60-69 years old	113/10100 1.1%	101/10095 1.0%	1.12 (0.86, 1.46)
70-79 years old	115/7351 1.6%	132/7333 1.8%	0.87 (0.68, 1.11)
≥80 years old	27/1220 2.2%	21/1289 1.6%	1.36 (0.78, 2.37)
AE Monitoring Substudy Cohort	64/3326	41/3249	1.53
(60 years of age and older)	1.9%	1.3%	(1.04, 2.25)
60-69 years old	22/1726 1.3%	18/1709 1.1%	1.21 (0.66, 2.23)
70-79 years old	31/1383 2.2%	19/1367 1.4%	1.61 (0.92, 2.82)
≥80 years old	11/217 5.1%	4/173 2.3%	2.19 (0.75, 6.45)

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

Among reported serious adverse events in the SPS (Days 0 to 42 postvaccination), serious cardiovascular events occurred more frequently in subjects who received ZOSTAVAX (20 [0.6%]) than in subjects who received placebo (12 [0.4%]) in the AE Monitoring Substudy. The frequencies of serious cardiovascular events were similar in subjects who received ZOSTAVAX (81 [0.4%]) and in subjects who received placebo (72 [0.4%]) in the entire study cohort (Days 0 to 42 postvaccination).

Serious Adverse Events Occurring Over the Entire Course of the Study

Rates of hospitalization were similar among subjects who received ZOSTAVAX and subjects who received placebo in the AE Monitoring Substudy, throughout the entire study.

Fifty-one individuals (1.5%) receiving ZOSTAVAX were reported to have congestive heart failure (CHF) or pulmonary edema compared to 39 individuals (1.2%) receiving placebo in the AE Monitoring Substudy; 58 individuals (0.3%) receiving ZOSTAVAX were reported to have congestive heart failure (CHF) or pulmonary edema compared to 45 (0.2%) individuals receiving placebo in the overall study.

In the SPS, all subjects were monitored for vaccine-related SAEs. Investigator-determined, 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).

Deaths

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

Most Common Adverse Reactions and Experiences in the AE Monitoring Substudy of the SPS

Injection-site adverse reactions reported at an incidence $\geq 1\%$ are shown in Table 3. Most of these adverse reactions were reported as mild in intensity. The overall incidence of vaccine-related injection-site adverse reactions was significantly greater for subjects vaccinated with ZOSTAVAX versus subjects who received placebo (48% for ZOSTAVAX and 17% for placebo).

Table 3: Injection-Site Adverse Reactions* in $\geq 1\%$ of Adults Who Received ZOSTAVAX or Placebo Within 5 Days Postvaccination from the AE Monitoring Substudy of the Shingles Prevention Study

Adverse Reaction	ZOSTAVAX (N = 3345) %	Placebo (N = 3271) %
<i>Solicited</i> [†]		
Erythema	35.6	6.9
Pain/Tenderness	34.3	8.3
Swelling	26.1	4.5
<i>Unsolicited</i>		
Hematoma	1.6	1.4
Pruritus	6.9	1.0
Warmth	1.6	0.3

*Patients instructed to report adverse experiences on a Vaccination Report Card

[†]Solicited on the Vaccination Report Card

Headache was the only systemic adverse reaction reported on the vaccine report card between Days 0-42 by $\geq 1\%$ of subjects in the AE Monitoring Substudy in either vaccination group (ZOSTAVAX 1.4%, placebo 0.8%).

The numbers of subjects with elevated temperature ($\geq 38.3^\circ\text{C}$ [$\geq 101.0^\circ\text{F}$]) within 42 days postvaccination were similar in the ZOSTAVAX and the placebo vaccination groups [27 (0.8%) vs. 27 (0.9%), respectively].

The following adverse experiences in the AE Monitoring Substudy of the SPS (Days 0 to 42 postvaccination) were reported at an incidence $\geq 1\%$ and greater in subjects who received ZOSTAVAX than in subjects who received placebo, respectively: respiratory infection (65 [1.9%] vs. 55 [1.7%]), fever (59 [1.8%] vs. 53 [1.6%]), flu syndrome (57 [1.7%] vs. 52 [1.6%]), diarrhea (51 [1.5%] vs. 41 [1.3%]), rhinitis (46 [1.4%] vs. 36 [1.1%]), skin disorder (35 [1.1%] vs. 31 [1.0%]), respiratory disorder (35 [1.1%] vs. 27 [0.8%]), asthenia (32 [1.0%] vs. 14 [0.4%]).

6.2 VZV Rashes Following Vaccination

Within the 42-day postvaccination reporting period in the ZEST, noninjection-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 in the ZOSTAVAX group; however, the virus strain (wild-type or Oka/Merck strain) could not be determined.

Within the 42-day postvaccination reporting period in the SPS, noninjection-site zoster-like rashes were reported by 53 subjects (17 for ZOSTAVAX and 36 for placebo). Of 41 specimens that were adequate for Polymerase Chain Reaction (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. Of reported varicella-like rashes (n=59), 10 had specimens that were available and adequate for PCR testing. VZV was not detected in any of these specimens.

In 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 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.

6.3 Post-Marketing Experience

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

Gastrointestinal disorders: nausea

Infections and infestations: vaccine strain herpes zoster; disseminated vaccine strain varicella-zoster virus disease including fatal outcomes in immunocompromised patients

Skin and subcutaneous tissue disorders: rash

Musculoskeletal and connective tissue disorders: arthralgia; myalgia

General disorders and administration site conditions: injection-site rash; pyrexia; injection-site urticaria; 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 Adverse Events

The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967 or report online to www.vaers.hhs.gov. {2}

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

In a randomized clinical study, a reduced immune response to ZOSTAVAX as measured by gpELISA was observed in individuals who received concurrent administration of PNEUMOVAX® 23 and ZOSTAVAX compared with individuals who received these vaccines 4 weeks apart. Consider administration of the two vaccines separated by at least 4 weeks [see *Clinical Studies (14.4)*].

For concomitant administration of ZOSTAVAX with inactivated influenza vaccine [see *Clinical Studies (14.4)*].

7.2 Antiviral Medications

Concurrent administration of ZOSTAVAX and antiviral medications known to be effective against VZV has not been evaluated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ZOSTAVAX is contraindicated for use in pregnant women because the vaccine contains live, attenuated varicella-zoster virus, and it is known that wild-type varicella-zoster virus, if acquired during pregnancy, can cause congenital varicella syndrome [see *Contraindications (4.3)* and *Patient Counseling Information (17)*].

Available data on inadvertent administration of ZOSTAVAX to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

It is not known whether varicella-zoster vaccine virus is excreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZOSTAVAX, and any potential adverse effects on the breastfed child from ZOSTAVAX or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

ZOSTAVAX is not indicated for prevention of primary varicella infection (Chickenpox) and should not be used in children and adolescents.

8.5 Geriatric Use

The median 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.

11 DESCRIPTION

ZOSTAVAX is a lyophilized preparation of the Oka/Merck strain of live, attenuated varicella-zoster virus (VZV). ZOSTAVAX, when reconstituted as directed, is a sterile suspension for subcutaneous administration. Each 0.65-mL dose contains a minimum of 19,400 PFU (plaque-forming units) of Oka/Merck strain of VZV when reconstituted and stored at room temperature for up to 30 minutes.

Each dose contains 31.16 mg of sucrose, 15.58 mg of hydrolyzed porcine gelatin, 3.99 mg of sodium chloride, 0.62 mg of monosodium L-glutamate, 0.57 mg of sodium phosphate dibasic, 0.10 mg of potassium phosphate monobasic, 0.10 mg of potassium chloride; residual components of MRC-5 cells including DNA and protein; and trace quantities of neomycin and bovine calf serum. The product contains no preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The risk of developing zoster appears to be 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 *Clinical Studies (14)*.]

Herpes zoster (HZ), commonly known as shingles or zoster, is a manifestation of the reactivation of varicella zoster virus (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. Zoster is characterized by a unilateral, painful, vesicular cutaneous eruption with a dermatomal distribution.

Pain associated with zoster may occur during the prodrome, the acute eruptive phase, and the postherpetic phase of the infection. Pain occurring in the postherpetic phase of infection is commonly referred to as postherpetic neuralgia (PHN).

Serious complications, such as PHN, scarring, bacterial superinfection, allodynia, cranial and motor neuron palsies, pneumonia, encephalitis, visual impairment, hearing loss, and death can occur as the result of zoster.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

In two large clinical trials (ZEST and SPS), ZOSTAVAX significantly reduced the risk of developing zoster when compared with placebo (see Table 4 and Table 5).

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

Efficacy of ZOSTAVAX was evaluated in the ZOSTAVAX Efficacy and Safety Trial (ZEST), a placebo-controlled, double-blind clinical trial in which 22,439 subjects 50 to 59 years of age were randomized to receive a single dose of either ZOSTAVAX (n=11,211) or placebo (n=11,228). Subjects were followed for the development of zoster for a median of 1.3 years (range 0 to 2 years). Confirmed zoster cases were determined by Polymerase Chain Reaction (PCR) [86%] or, in the absence of virus detection, by a Clinical Evaluation Committee [14%]. The primary efficacy analysis included all subjects randomized in the study (intent-to-treat [ITT] analysis).

Compared with placebo, ZOSTAVAX significantly reduced the risk of developing zoster by 69.8% (95% CI: 54.1, 80.6%) in subjects 50 to 59 years of age (Table 4).

Table 4: Efficacy of ZOSTAVAX on HZ Incidence Compared with Placebo in the ZOSTAVAX Efficacy and Safety Trial*

Age group (yrs.)	ZOSTAVAX			Placebo			Vaccine Efficacy (95% CI)
	# subjects	# HZ cases	Incidence rate of HZ per 1000 person-yrs.	# subjects	# HZ cases	Incidence rate of HZ per 1000 person-yrs.	
50-59	11211	30	1.994	11228	99	6.596	69.8% (54.1%, 80.6%)

*The analysis was performed on the intent-to-treat (ITT) population that included all subjects randomized in the ZEST study.

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 study. VZV antibody levels (Geometric Mean Titers, GMT), as measured by glycoprotein enzyme-linked immunosorbent assay (gpELISA) 6 weeks postvaccination, were increased 2.3-fold (95% CI: 2.2, 2.4) in the group of subjects who received ZOSTAVAX compared to subjects who received placebo; the specific antibody level that correlates with protection from zoster has not been established.

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

Efficacy of ZOSTAVAX was evaluated in the Shingles Prevention Study (SPS), a placebo-controlled, double-blind clinical trial in which 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). Subjects were followed for the development of zoster for a median of 3.1 years (range 31 days to 4.90 years). The study excluded people who were immunocompromised or using corticosteroids on a regular basis, anyone with a previous history of HZ, and those with conditions that might interfere with study evaluations, including people with cognitive impairment, severe hearing loss, those who were non-ambulatory, and those whose survival was not considered to be at least 5 years. Randomization was stratified by age, 60-69 and ≥70 years of age. Suspected zoster cases were confirmed by Polymerase Chain Reaction (PCR) [93%], viral culture [1%], or in the absence of virus detection, as determined by a Clinical Evaluation Committee [6%]. Individuals in both vaccination groups who developed zoster were given famciclovir, and, as necessary, pain medications. The primary efficacy analysis included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of HZ within the first 30 days postvaccination (Modified Intent-To-Treat [MITT] analysis).

ZOSTAVAX significantly reduced the risk of developing zoster when compared with placebo (Table 5). In the SPS, vaccine efficacy for the prevention of HZ was highest for those subjects 60-69 years of age and declined with increasing age.

Table 5: Efficacy of ZOSTAVAX on HZ Incidence Compared with Placebo in the Shingles Prevention Study*

Age group† (yrs.)	ZOSTAVAX			Placebo			Vaccine Efficacy (95% CI)
	# subjects	# HZ cases	Incidence rate of HZ per 1000 person-yrs.	# subjects	# HZ cases	Incidence rate of HZ per 1000 person-yrs.	
Overall	19254	315	5.4	19247	642	11.1	51% (44%, 58%)
60-69	10370	122	3.9	10356	334	10.8	64% (56%, 71%)
70-79	7621	156	6.7	7559	261	11.4	41% (28%, 52%)
≥80	1263	37	9.9	1332	47	12.2	18% (-29%, 48%)

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

† Age strata at randomization were 60-69 and ≥70 years of age.

Forty-five subjects were excluded from the MITT analysis (16 in the group of subjects who received ZOSTAVAX and 29 in the group of subjects who received placebo), including 24 subjects with evaluable HZ cases that occurred in the first 30 days postvaccination (6 evaluable HZ cases in the group of subjects who received ZOSTAVAX and 18 evaluable HZ cases in the group of subjects who received placebo).

Suspected HZ cases were followed prospectively for the development of HZ-related complications. Table 6 compares the rates of PHN defined as HZ-associated pain (rated as 3 or greater on a 10-point scale by the study subject and occurring or persisting at least 90 days) following the onset of rash in evaluable cases of HZ.

Table 6: Postherpetic Neuralgia (PHN)* in the Shingles Prevention Study†

Age group (yrs.)‡	ZOSTAVAX					Placebo					Vaccine efficacy against PHN in subjects who develop HZ postvaccination (95% CI)
	# subjects	# HZ cases	# PHN cases	Incidence rate of PHN per 1,000 person-yrs.	% HZ cases with PHN	# subjects	# HZ cases	# PHN cases	Incidence rate of PHN per 1,000 person-yrs.	% HZ cases with PHN	
Overall	19254	315	27	0.5	8.6%	19247	642	80	1.4	12.5%	39%§ (7%, 59%)
60-69	10370	122	8	0.3	6.6%	10356	334	23	0.7	6.9%	5% (-107%, 56%)
70-79	7621	156	12	0.5	7.7%	7559	261	45	2.0	17.2%	55% (18%, 76%)
≥80	1263	37	7	1.9	18.9%	1332	47	12	3.1	25.5%	26% (-69%, 68%)

* PHN was defined as HZ-associated pain rated as ≥3 (on a 0-10 scale), persisting or appearing more than 90 days after onset of HZ rash using Zoster Brief Pain Inventory (ZBPI). {5}

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

‡ Age strata at randomization were 60-69 and ≥70 years of age.

§ Age-adjusted estimate based on the age strata (60-69 and ≥70 years of age) at randomization.

The median duration of clinically significant pain (defined as ≥3 on a 0-10 point scale) among HZ cases in the group of subjects who received ZOSTAVAX as compared to the group of subjects who received placebo was 20 days vs. 22 days based on the confirmed HZ cases.

Overall, the benefit of ZOSTAVAX in the prevention of PHN can be primarily attributed to the effect of the vaccine on the prevention of herpes zoster. Vaccination with ZOSTAVAX in the SPS reduced the incidence of PHN in individuals 70 years of age and older who developed zoster postvaccination. Other prespecified zoster-related complications were reported less frequently in subjects who received ZOSTAVAX compared to subjects who received placebo. Among HZ cases, zoster-related complications were reported at similar rates in both vaccination groups (Table 7).

Table 7: Specific complications* of zoster among HZ cases in the Shingles Prevention Study

Complication	ZOSTAVAX (N = 19270)		Placebo (N = 19276)	
	(n = 321)	% Among Zoster Cases	(n = 659)	% Among Zoster Cases
Allodynia	135	42.1	310	47.0
Bacterial Superinfection	3	0.9	7	1.1
Dissemination	5	1.6	11	1.7
Impaired Vision	2	0.6	9	1.4
Ophthalmic Zoster	35	10.9	69	10.5
Peripheral Nerve Palsies (motor)	5	1.6	12	1.8
Ptosis	2	0.6	9	1.4
Scarring	24	7.5	57	8.6
Sensory Loss	7	2.2	12	1.8

N=number of subjects randomized

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

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

Visceral complications reported by fewer than 1% of subjects with zoster included 3 cases of pneumonitis and 1 case of hepatitis in the placebo group, and 1 case of meningoencephalitis in the vaccine group.

Immune responses to vaccination were evaluated in a subset of subjects enrolled in the Shingles Prevention Study (N=1,395). VZV antibody levels (Geometric Mean Titers, GMT), as measured by glycoprotein enzyme-linked immunosorbent assay (gpELISA) 6 weeks postvaccination, were increased 1.7-fold (95% CI: 1.6 to 1.8) in the group of subjects who received ZOSTAVAX compared to subjects who received placebo; the specific antibody level that correlates with protection from zoster has not been established.

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

An interim analysis of a prospective observational cohort study conducted in a US integrated healthcare system database estimated vaccine effectiveness against HZ and PHN among 1,355,720 individuals 50 years of age and older, including 392,677 who received ZOSTAVAX. Age eligible individuals contributed person-time to the unvaccinated group and, once vaccinated with ZOSTAVAX, contributed person-time to the vaccinated group for the remainder of the study. Vaccine effectiveness (VE) against HZ and PHN was calculated using the incidence rates of protocol-defined first episode of HZ and PHN in the vaccinated and unvaccinated groups, including adjustments for calendar time, age, sex, race/ethnicity, healthcare resource utilization, comorbid conditions, and immunocompromise status. The gender and racial/ethnic distributions of study individuals were overall 53% female, 60% white, 15% Asian or Pacific Islander, 13% Hispanic, and 7% black or African American.

For individuals 50-59 years of age at the time of vaccination, the average VE against HZ over the first 3 years following vaccination was 60% (95% CI: 52, 66), with VE against HZ of 36% (95% CI: -55, 73) in the third year post-vaccination. For individuals 60-69 years of age, 70-79 years of age, and 80 years of age and older at the time of vaccination, the average VE against HZ over the first 5 years following vaccination was 49% (95% CI: 47, 52), 46% (95% CI: 43, 48), and 44% (95% CI: 38, 49), respectively, with VE against HZ of 34% (95% CI: 25, 42), 29% (95% CI: 18, 38), and 36% (95% CI: 12, 53), respectively, in the fifth year post-vaccination. Follow-up time for individuals 50-59 years of age was shorter because ZOSTAVAX was approved for use in this age group five years after approval for use in individuals 60 years of age and older.

Insufficient data were available at the time of the interim analysis to assess the outcome of PHN in individuals 50-59 years of age. For individuals 60-69 years of age, 70-79 years of age, and 80 years of age and older at the time of vaccination, the average VE against PHN over the first 5 years following vaccination was 72% (95% CI: 65, 77), 69% (95% CI: 62, 75), and 61% (95% CI: 47, 71), respectively, with VE against PHN of 61% (95% CI: 33, 77), 69% (95% CI: 44, 82), and 34% (95% CI: -49, 71), respectively, in the fifth year post-vaccination. The benefit of ZOSTAVAX in the prevention of PHN can be attributed in part to the effect of the vaccine on the prevention of HZ.

14.4 Concomitant Use Studies

In a double-blind, controlled substudy, 374 adults in the US, 60 years of age and older (median age = 66 years), were randomized to receive trivalent inactivated influenza vaccine (TIV) and ZOSTAVAX concurrently (N=188), or TIV alone followed 4 weeks later by ZOSTAVAX alone (N=186). The antibody responses to both vaccines at 4 weeks postvaccination were similar in both groups.

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 randomized to receive ZOSTAVAX and PNEUMOVAX 23 concomitantly (N=237), or PNEUMOVAX 23 alone followed 4 weeks later by ZOSTAVAX alone (N=236). At 4 weeks postvaccination, the VZV antibody levels following concomitant use were significantly lower than the VZV antibody levels following nonconcomitant administration (GMTs of 338 vs. 484 gpELISA units/mL, respectively; GMT ratio = 0.70 (95% CI: 0.61, 0.80).

15 REFERENCES

1. Reitschel RL, Bernier R. Neomycin sensitivity and the MMR vaccine. JAMA 1981;245(6):571.
2. Atkinson WL, Pickering LK, Schwartz B, Weniger BG, Iskander JK, Watson JC. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2002;51(RR02):1-36.
3. Rynn L, Cragan J, Correa A. Update on Overall Prevalence of Major Birth Defects-Atlanta, Georgia,1978-2005. CDC MMWR January 11, 2008/57(01);1-5.
4. American College of Obstetricians and Gynecologists Frequently Asked Questions: Miscarriage and Molar Pregnancy; 2011.
5. Coplan PM, Schmader K, Nikas A, Chan ISF, Choo P, Levin MJ, 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 4963-00 — ZOSTAVAX is supplied as follows: (1) a package of 1 single-dose vial of lyophilized vaccine, **NDC 0006-4963-00** (package A); and (2) a separate package of 10 vials of diluent (package B).

No. 4963-41 — ZOSTAVAX is supplied as follows: (1) a package of 10 single-dose vials of lyophilized vaccine, **NDC 0006-4963-41** (package A); and (2) a separate package of 10 vials of diluent (package B).

Storage

To maintain potency, ZOSTAVAX must be stored frozen between -58°F and +5°F (-50°C and -15°C). Use of dry ice may subject ZOSTAVAX to temperatures colder than -58°F (-50°C).

Before reconstitution, ZOSTAVAX SHOULD BE STORED FROZEN at a temperature between -58°F and +5°F (-50°C and -15°C) until it is reconstituted for injection. Any freezer, including frost-free, that has a separate sealed freezer door and reliably maintains an average temperature between -58°F and +5°F (-50°C and -15°C) is acceptable for storing ZOSTAVAX. Routine defrost cycling of a frost-free freezer is acceptable.

ZOSTAVAX may be stored and/or transported at refrigerator temperature between 36°F and 46°F (2°C to 8°C) for up to 72 continuous hours prior to reconstitution. Vaccine stored between 36°F and 46°F (2°C to 8°C) that is not used within 72 hours of removal from +5°F (-15°C) storage should be discarded. ZOSTAVAX should be reconstituted immediately upon removal from the freezer. The diluent should be stored separately at room temperature (68°F to 77°F, 20°C to 25°C), or in the refrigerator (36°F to 46°F, 2°C to 8°C).

For information regarding the product or questions regarding storage conditions, call 1-800-MERCK-90.


Before reconstitution, protect from light.

DO NOT FREEZE RECONSTITUTED VACCINE.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- Question the patient about reactions to previous vaccines.
- Provide a copy of the patient information (PPI) located at the end of this insert and discuss any questions or concerns.
- Inform patient of the benefits and risks of ZOSTAVAX, including the potential risk of transmitting the vaccine virus to susceptible individuals, such as immunosuppressed or immunodeficient individuals or pregnant women who have not had chickenpox.
- Instruct patient to report any adverse reactions or any symptoms of concern to their healthcare professional.

Dist. by: Merck Sharp & Dohme Corp., a subsidiary of
 **MERCK & CO., INC., Whitehouse Station, NJ 08889, USA**

For patent information: www.merck.com/product/patent/home.html

Copyright © 2006-2019 Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.**
All rights reserved.

uspi-v211-i-fro-1901r027