ZOSTAVAX
Zoster Vaccine Live (Oka/Merck)
Refrigerator stable

I. THERAPEUTIC CLASS

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

II. INDICATIONS

ZOSTAVAX is indicated for:
• Prevention of herpes zoster (shingles)
• Prevention of postherpetic neuralgia (PHN)

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

III. DOSAGE AND ADMINISTRATION

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FOR SUBCUTANEOUS ADMINISTRATION.

Do not inject intravascularly.

Individuals should receive a single dose. At present, the duration of protection after vaccination with ZOSTAVAX is unknown. In the Shingles Prevention Study (SPS), protection was demonstrated through 4 years of follow-up. The need for revaccination has not yet been defined.

ZOSTAVAX is not a treatment for zoster or PHN.

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

Reconstitute immediately upon removal from the refrigerator.

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

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

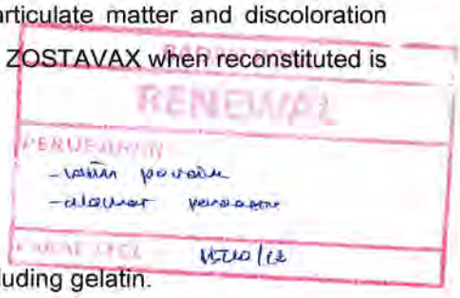
IT IS RECOMMENDED THAT THE VACCINE BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION, TO MINIMIZE LOSS OF POTENCY. DISCARD RECONSTITUTED VACCINE IF IT IS NOT USED WITHIN 30 MINUTES.

Do not freeze reconstituted vaccine.
CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of ZOSTAVAX because these substances may inactivate the vaccine virus.

A separate sterile needle and syringe should be used for administration of ZOSTAVAX to prevent transfer of infectious diseases.

Needles should be disposed of properly and should not be recapped.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. ZOSTAVAX when reconstituted is a semi-hazy to translucent, off white to pale yellow liquid.



IV. CONTRAINDICATIONS

History of hypersensitivity to any component of the vaccine, including gelatin.

History of anaphylactic/anaphylactoid reaction to neomycin (each dose of reconstituted vaccine contains trace quantities of neomycin). Neomycin allergy generally manifests as a contact dermatitis. However, a history of contact dermatitis due to neomycin is not a contraindication to receiving live virus vaccines.

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

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 **XVII. CLINICAL PHARMACOLOGY**); cellular immune deficiencies.

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

Active untreated tuberculosis.

Pregnancy (see **VI. PREGNANCY**).

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V. PRECAUTIONS

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

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

Deferral of vaccination should be considered in the presence of fever >38.5°C (>101.3°F).

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

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 vaccines who develop a varicella-like rash and susceptible contacts. Transmission of vaccine virus from varicella vaccine recipients who do not

develop a varicella-like rash has also been reported. This is a theoretical risk for vaccination with ZOSTAVAX. The risk of transmitting the attenuated vaccine virus to a susceptible individual should be weighed against the risk of developing natural zoster that could be transmitted to a susceptible individual.

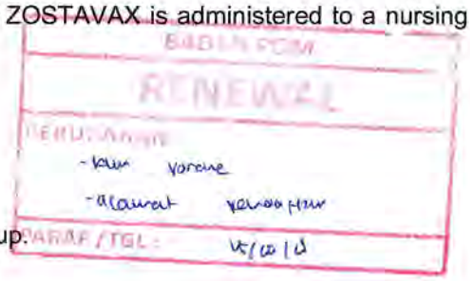
VI. PREGNANCY

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

Pregnancy Category C

VII. NURSING MOTHERS

It is not known whether VZV is secreted in human milk. Therefore, because some viruses are secreted in human milk, caution should be exercised if ZOSTAVAX is administered to a nursing woman.



VIII. PEDIATRIC USE

ZOSTAVAX is not recommended for use in this age group.

IX. GERIATRIC USE

The mean age of subjects enrolled in the largest (N=38,546) clinical study of ZOSTAVAX was 69 years (range 59-99 years). Of the 19,270 subjects who received ZOSTAVAX, 10,378 were 60-69 years of age, 7,629 were 70-79 years of age, and 1,263 were 80 years of age or older. ZOSTAVAX was demonstrated to be generally safe and effective in this population.

X. DRUG INTERACTIONS

ZOSTAVAX must not be mixed with any other medicinal product in the same syringe. Other medicinal products must be given as separate injections and at different body sites.

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

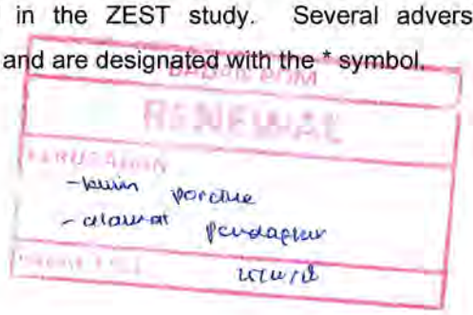
XI. SIDE EFFECTS

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 postvaccination in addition to undergoing routine safety monitoring throughout the study.

The following very common (≥1/10) and common (≥1/100, <1/10) vaccine-related injection-site and systemic adverse experiences were reported in the ZEST study. Several adverse experiences were solicited (Days 1-5 postvaccination) and are designated with the * symbol.



Nervous system disorder
Common: headache

General disorders and administration site conditions
Very common: erythema,* pain,* swelling*, pruritus
Common: hematoma, warmth, induration

Musculoskeletal and connective tissue disorders
Common: pain in extremity

The overall incidence of vaccine-related injection-site adverse experiences was significantly greater for subjects vaccinated with ZOSTAVAX versus subjects who received placebo (63.9% for ZOSTAVAX and 14.4% for placebo).

Within the 42-day post vaccination reporting period in the ZEST, noninjection-site zosteriform rashes were reported by 34 subjects (19 for ZOSTAVAX and 15 for placebo). Of 24 specimens that were adequate for Polymerase Chain Reaction (PCR) testing, wild-type VZV was detected in 10 (3 for ZOSTAVAX, 7 for placebo) of these specimens. The Oka/Merck strain of VZV was not detected from any of these specimens.

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

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

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

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

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

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Nervous system disorder

Common: headache

General disorders and administration site conditions

Very common: erythema,* pain/tenderness,* swelling*

Common: hematoma, pruritus, warmth

The overall incidence of vaccine-related injection-site adverse experiences was significantly greater for subjects vaccinated with ZOSTAVAX versus subjects who received placebo (48% for ZOSTAVAX and 17% for placebo).

The remainder of subjects in the SPS received routine safety monitoring, but were not provided report cards. The types of events reported in these patients were generally similar to the subgroup of patients in the Adverse Event Monitoring Substudy.

Within the 42-day 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 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.

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Other Studies

In other clinical trials in support of the initial licensure of the frozen formulation of ZOSTAVAX, the reported rates of noninjection-site zosteriform and varicella-like rashes within 42 days postvaccination were also low in both zoster vaccine recipients and placebo recipients. Of 17 reported varicella-like rashes and non-injection site zoster-like rashes, 10 specimens were available and adequate for PCR testing, and 2 subjects had varicella (onset Day 8 and 17) confirmed to be Oka/Merck strain.

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

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

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

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
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
Infections and infestations: herpes zoster (vaccine strain)
Eye Disorders: Necrotizing retinitis (patiens on immunosuppressive therapy)

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XII. OVERDOSAGE

There are no data with regard to overdose.

XIII. STORAGE

Shelf life: 18 months

Storage

During shipment, to ensure that there is no loss of potency, the vaccine must be maintained at a temperature of 8°C (46°F) or colder.

ZOSTAVAX **SHOULD BE STORED REFRIGERATED** at a temperature of 2 to 8°C (36 to 46°F) or colder until it is reconstituted for injection (see **III DOSAGE AND ADMINISTRATION**). The

diluent should be stored separately at room temperature (20 to 25°C, 68 to 77°F) or in the refrigerator (2 to 8°C, 36 to 46°F).

Before reconstitution, protect from light.

DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.

DO NOT FREEZE THE RECONSTITUTED VACCINE.

XIV. AVAILABILITY

Box, 1 single dose 0.65 mL & 1 single dose sterile diluent syringe.

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XV. CHEMISTRY

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

XVI. COMPOSITION

XVIa. Active Ingredients

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

XVIb. Inactive Ingredients

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

XVII. CLINICAL PHARMACOLOGY

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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. Zoster is usually characterized by a unilateral, painful, vesicular cutaneous eruption with a dermatomal distribution.

Although the blistering rash is the most distinctive feature of zoster, the most frequently debilitating symptom is pain, which may occur during the prodrome, the acute eruptive phase, and the postherpetic phase of the infection. During the acute eruptive phase, local pain has been reported to occur in up to 90% of immunocompetent individuals.

Anyone who has been infected with VZV, including those without a clinical history of varicella, is at risk for developing zoster, which is considered to be due to waning immunity to VZV. Nearly all adults (~98%) in the U.S. are susceptible to zoster, where an estimated 1 million cases occur annually. This number is expected to rise as the mean age of the population increases. 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.

Seventy to 80% of hospitalizations for zoster occur among immunocompetent individuals. In the U.S., approximately 50,000 to 60,000 zoster-associated hospitalizations, including 12,000 to 19,000 in which the primary diagnosis is zoster, occur each year.

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

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

Postherpetic Neuralgia

Postherpetic neuralgia (PHN) constitutes the most common serious complication and cause of zoster-associated morbidity in the immunocompetent host. Published literature estimates the prevalence of PHN in the U.S. population to be 500,000 to 1,000,000 cases. 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 one of 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*.)

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Clinical Studies

Evaluation of Clinical Efficacy Afforded by ZOSTAVAX

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

In the ZOSTAVAX Efficacy and Safety Trial (ZEST), a placebo-controlled, double-blind clinical trial in which 22,439 subjects 50 to 59 years of age were randomized to receive a single dose of either ZOSTAVAX (n=11,211) or placebo (n=11,228) and were followed for the development of zoster for a median of 1.3 years (range 0 to 2 years). All suspected zoster cases were adjudicated by a clinical evaluation committee. Final determination of zoster cases was made by Polymerase Chain Reaction (PCR) [86%], or in the absence of virus detection, as determined by a clinical evaluation committee [14%].

ZOSTAVAX significantly decreased the incidence of zoster compared with placebo (30 cases [2.0/1000 person-years] vs. 99 cases [6.6/1000 person-years], respectively; $p<0.001$). The protective efficacy of ZOSTAVAX against zoster was 69.8% (95% CI: [54.1 to 80.6%]).

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

In the Shingles Prevention Study (SPS), a placebo-controlled, double-blind clinical trial of ZOSTAVAX, 38,546 subjects 60 years of age or older were randomized to receive a single dose of either ZOSTAVAX (n=19,270) or placebo (n=19,276) and were followed for the development of zoster for an average of 3.1 years (range 1 day to 4.9 years). Randomization was stratified by age, 60-69 and ≥70 years of age. All suspected zoster cases were adjudicated by a clinical

evaluation committee. Final determination of zoster cases was made by PCR, local culture, or the decision of the clinical evaluation committee, in that order. In both vaccination groups (ZOSTAVAX and placebo), subjects who developed zoster were given famciclovir, and as necessary, pain medications. Severity of pain was evaluated according to a "worst pain" score on a 0-to-10 scale, using the Zoster Brief Pain Inventory (ZBPI), a validated questionnaire. Ascore 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.)

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

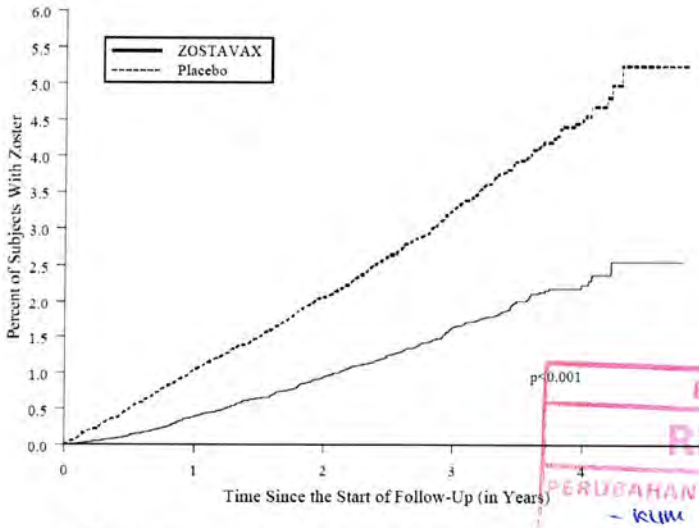
Endpoint	Vaccine efficacy	95% CI
Incidence of Zoster	51%	44 to 58%
Incidence of PHN*	67%	48 to 79%
HZ Pain BOI**	61%	51 to 69%

*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 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.

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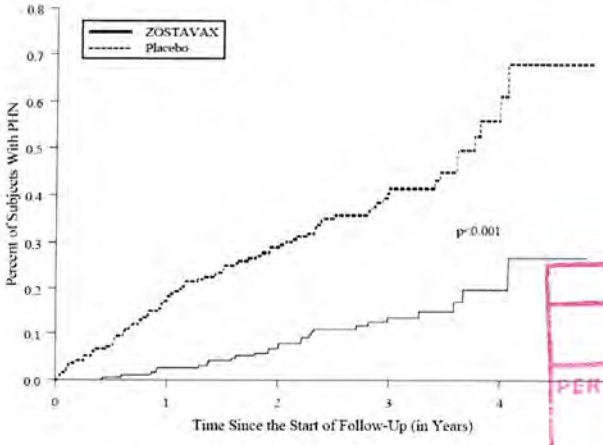
ZOSTAVAX decreased the incidence of PHN compared with placebo (27 cases [0.5/1000 person-years] vs. 80 cases [1.4/1000 person-years], respectively; p<0.001). In this trial, the definition of PHN was clinically significant zoster-associated pain persisting or appearing at least 90 days after the onset of rash. The protective efficacy of ZOSTAVAX against PHN was 67% (95% CI: [48 to 79%]), and the reduction was similar for the two age groups (60-69 and ≥70 years of age). The absolute efficacy was 0.2%. In addition, the efficacy of ZOSTAVAX did not change appreciably when PHN was defined using alternative cutoff times (30, 60, 120, or 182 days) for duration of pain. ZOSTAVAX significantly reduced the cumulative incidence of PHN over time compared with placebo (p<0.001; 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.

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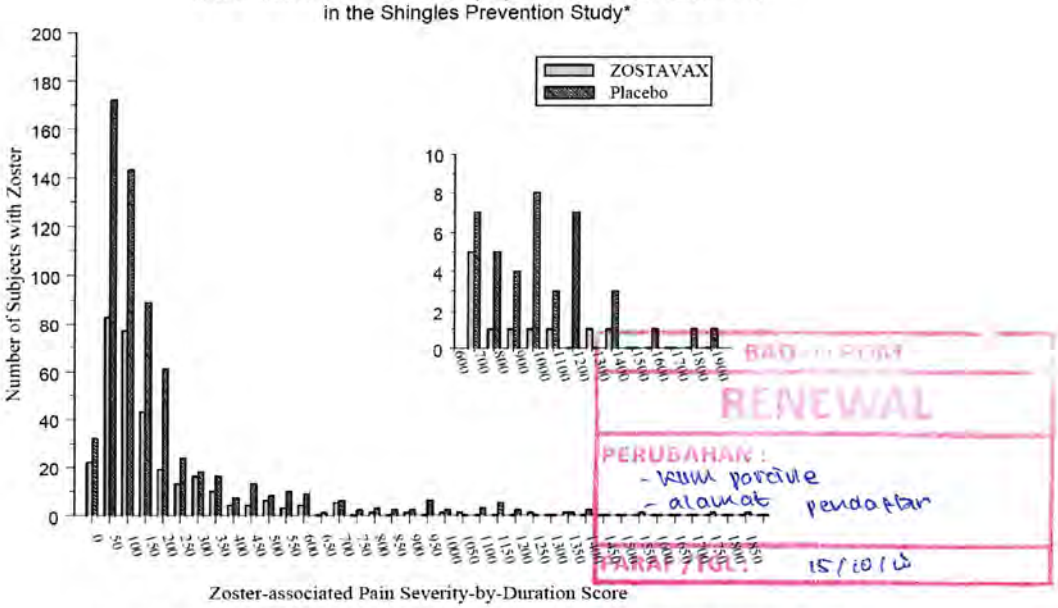
ZOSTAVAX reduced the HZ pain BOI score by approximately 61% (95% CI: [51 to 69%]), compared with placebo. ZOSTAVAX reduced the HZ pain BOI score to a similar extent for the two age groups (60-69 and ≥70 years of age). The HZ pain BOI score is a composite score that incorporates the incidence, severity, 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 favorable, but not statistically significant, 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. 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

Within the ZOSTAVAX Efficacy and Safety Trial (ZEST), immune responses to vaccination were evaluated in a random 10% subcohort (n=1,136 for ZOSTAVAX and n=1,133 for placebo) of the subjects enrolled in the ZEST. ZOSTAVAX elicited higher VZV-specific immune responses at 6 weeks postvaccination compared with placebo. Increases in VZV antibody level, measured by glycoprotein enzyme-linked immunosorbent assay (gpELISA) were demonstrated (2.3-fold difference (95% CI [2.2, 2.4]), geometric mean titer [GMT] of 664 vs. 288 gpELISA units/mL, p <0.001).

RENEWAL
PERUBAHAN :
- kaum porsine
- alamat pendaftar
15/10/18

Within the Shingles Prevention Study (SPS), immune responses to vaccination were evaluated in a subset of the enrolled subjects (N=1395). ZOSTAVAX elicited higher VZV-specific immune responses at 6 weeks postvaccination compared with placebo. Increases in both VZV antibody level, measured by glycoprotein enzyme-linked immunosorbent assay (gpELISA) (1.7 fold difference, geometric mean titer [GMT] of 479 vs. 288 gpELISA units/mL, p <0.001), and T-cell activity, measured by VZV interferon-gamma enzyme-linked immunospot (IFN-γ ELISPOT) assay (2.2 fold-difference, geometric mean count [GMC] of 70 vs. 32 spot-forming cells per million peripheral blood mononuclear cells [SFC/106 PBMCs], p<0.001) were demonstrated.

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

Immunogenicity following concomitant administration

In a double-blind, controlled clinical trial, 762 adults 50 years of age and older were randomized to receive a single dose of ZOSTAVAX administered either concomitantly (N=382) or nonconcomitantly (N=380) with inactivated influenza vaccine. Subjects enrolled in the concomitant group received ZOSTAVAX and influenza vaccine on Day 1 and placebo at Week 4. Subjects enrolled in the nonconcomitant group received influenza vaccine and placebo on Day 1 and ZOSTAVAX at Week 4. The antibody responses to both vaccines at 4 weeks postvaccination were similar, whether administered concomitantly or nonconcomitantly.

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

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX was administered to 100 subjects 50 years of age or older with a history of herpes zoster (HZ) prior to vaccination to assess immunogenicity of ZOSTAVAX. ZOSTAVAX induced a significantly higher VZV-specific immune response as measured by gpELISA at 4 weeks postvaccination, compared with placebo (2.1-fold difference (95% CI: [1.5 to 2.9], p<0.001), GMT of 812 vs. 393 gpELISA units/ml). VZV antibody responses were generally similar in subjects 50 to 59 compared to subjects ≥60 years of age.

BADAN POM
RENEWAL
PERUBAHAN
- lain lain
- alamat pendaftar
PARAF / TGL 15/10/16

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 **III. DOSAGE & ADMINISTRATION**). In this study, a total of 295 subjects received dose 1 and 286 subjects received dose 2. Compared with placebo, ZOSTAVAX induced a higher VZV-specific gpELISA antibody GMT at Week 6 (6 weeks following dose 1) and Week 12 (6 weeks following dose 2) (GMT of 534.4 and 530.3 vs. 263.7 and 250.3 gpELISA units/ml, respectively). The geometric mean fold-rises of the VZV antibody response, as measured by gpELISA, from baseline to Week 6 and Week 12 were 1.78 (95% CI: [1.64 to 1.92]) and 1.80 (95% CI: [1.66 to 1.95]), respectively, in vaccine recipients and 1.05 (95% CI: [0.98 to 1.12]) and 1.04 (95% CI: [0.96 to 1.13]), respectively, in placebo recipients. (See **IV. CONTRAINDICATIONS** regarding immunosuppression due to HIV/AIDS.)

XVIII. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data to suggest that ZOSTAVAX affects the ability to drive or operate machinery.

XIX. INFORMATION FOR PATIENTS

The health care provider should inform the patient of the benefits and risks of ZOSTAVAX. Patients should be instructed to report any adverse reactions to their health care provider. Pregnancy should be avoided for three months following vaccination.

BADAN POM
RENEWAL
PERUBAHAN
- kuur Vaccine
- alamat perdaftar
PARAF /TGL : 15/10/16

XX. ANIMAL TOXICOLOGY

XXa. Carcinogenesis, Mutagenesis, Reproduction

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

Mengandung Babi

HARUS DENGAN RESEP DOKTER

Registration No.

Box, 1 single dose 0.65 mL & 1 single dose sterile diluent syringe, Reg. No. DKI1463500244A1

Manufactured by:

Merck Sharp & Dohme Corp.,

West Point, PA. 19486, U.S.A

Packaged by:

Merck Sharp Dohme B.V

Haarlem. Netherlands

Registered by:

PT. Merck Sharp Dohme Pharma Tbk

Pasuruan, Jawa Timur

BADAN POM

RENEWAL

PERUBAHAN :

- nama perusahaan
- alamat perusahaan

PARAF /TGL :

PI version 7.0

S-WPC-V211-R-I-062017

MSD

Informasi Untuk Pasien Tentang ZOSTAVAX™
Zoster Vaccine Live (Oka/Merck)
Refrigerator stable

Apa itu ZOSTAVAX?

ZOSTAVAX, Zoster Vaccine Live (Oka/Merck), adalah vaksin injeksi virus hidup

ZOSTAVAX mengandung beberapa zat tambahan sebagai berikut:

Sucrose

Gelatine

Urea

Sodium Chloride

Monosodium L-Glutamate Monohydrate

Sodium Phosphate Dibasic

Potassium Phosphate Monobasic

Potassium Chloride

BADAN POM
RENEWAL
PERUBAHAN :
- alamat pendaftar
PARAF /TGL

Bentuk sediaan ZOSTAVAX:

Dus, 1 vial @ 19.400 PFU + 1 syringe pelarut

Pemegang Izin Produk:

PT Merck Sharp Dohme Pharma Tbk

Pasuruan, Jawa Timur

Produsen:

Merck Sharp & Dohme Corp.,

West Point, PA 19486, USA

Dikemas oleh:

Merck Sharp & Dohme B.V.

Haarlem, Netherlands

Mengapa dokter saya meresepkan ZOSTAVAX?

Dokter Anda telah menganjurkan atau memberikan ZOSTAVAX untuk membantu melindungi Anda terhadap cacar api (biasa dikenal dengan zoster).

Jika anda mengalami cacar api walaupun anda telah divaksinasi, ZOSTAVAX akan membantu melindungi dari nyeri saraf yang berkepanjangan setelah cacar api. ZOSTAVAX juga dapat mengurangi intensitas dan lama waktu dari nyeri yang terjadi.

ZOSTAVAX diberikan kepada orang dewasa 50 tahun ke atas.

ZOSTAVAX meningkatkan sistem imun untuk membantu melindungi anda dari cacar api.

Sama halnya dengan vaksin lain, ZOSTAVAX mungkin tidak melindungi seluruh orang yang mendapat vaksin ini.

ZOSTAVAX tidak dapat digunakan untuk mengobati cacar api yang sedang terjadi atau nyeri yang muncul bersama cacar api yang sedang terjadi.

ZOSTAVAX dapat diberikan bersamaan dengan vaksin influenza inaktif.

BADAN POM
RENEWAL
PERUBAHAN :
- nama perusahaan
- alamat pendaftar
PARAF / TGL : 25/10/18

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BADAN POM
RENEWAL
PERUBAHAN - 15/10/12
-vaksin Powder
-diluent Vendor Lain
PARAF / TGL

Mengapa saya menerima ZOSTAVAX?

Cacar api dapat menjadi sangat nyeri dan berpotensi menjadi penyakit yang melemahkan. Cacar api dapat mengakibatkan nyeri saraf berkepanjangan dan komplikasi serius lainnya. Merupakan penyakit yang tidak dapat diprediksi yang dapat terjadi kapan saja, tanpa peringatan sebelumnya. Hampir semua orang dewasa yang memiliki cacar air memiliki risiko untuk terkena cacar api. Risiko tersebut meningkat seiring dengan bertambahnya usia. Hal tersebut terutama jika anda berusia diatas 50 tahun. ZOSTAVAX merupakan satu-satunya produk yang disetujui untuk melindungi dari cacar api. Jika anda terkena cacar api bahkan setelah anda melakukan vaksinasi, ZOSTAVAX dapat membantu mengurangi intensitas dan lama waktu dari nyeri yang terjadi.

Apa itu cacar api?

Cacar api merupakan ruam melepuh dan menyakitkan yang dapat meninggalkan luka. Lepuhan dapat bertahan selama beberapa minggu. Bahkan dapat terjadi beberapa lepuhan sekaligus di dalam satu bagian tubuh. Nyeri saraf yang terjadi karena cacar api dapat bertahan selama beberapa bulan atau bahkan beberapa tahun setelah ruam pulih.

Apa penyebab cacar api?

Cacar api disebabkan oleh virus yang sama yang menyebabkan cacar air. Setelah lepuhan cacar air pulih, virus penyebabnya akan bertahan di tubuh anda, di dalam sistem saraf. Virus dapat berada disana selama beberapa tahun dan tidak menyebabkan masalah apapun. Namun, terkadang virus tersebut dapat berubah menjadi aktif kembali. Jika ini terjadi, dapat menyebabkan ruam yang melepuh dan nyeri.

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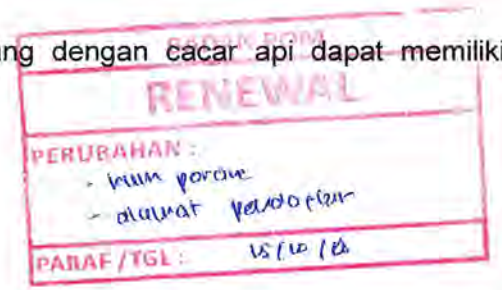
Apakah cacar api serius?

Cacar api bisa menjadi serius. Terkadang nyeri saraf akibat cacar api dapat menjadi parah dan bertahan hingga beberapa bulan bahkan tahun. Untuk beberapa orang, nyeri saraf ini dapat mengganggu aktifitas normal sehari-hari seperti berjalan, tidur, dan aktifitas sosial.

Nyeri akibat cacar api juga dapat berujung ke tekanan emosi. Orang yang menderita cacar api telah menggambarkan rasa nyeri mereka ke dalam beberapa cara. Beberapa mengatakan rasa nyeri membakar atau berdenyut. Beberapa lainnya mengatakan nyeri menusuk, menembak atau terasa tajam. Nyeri yang parah dapat diakibatkan oleh hal-hal kecil seperti hembusan angin atau sentuhan pakaian terhadap kulit.

Sebagai tambahan untuk nyeri yang parah, orang dengan cacar api dapat memiliki komplikasi lain. Termasuk:

- Bekas luka
- Infeksi bakteri di kulit
- Kelemahan
- lumpuh otot
- gangguan pendengaran dan pengelihatan



Cacar api dapat mengakibatkan perawatan di rumah sakit. Pada kasus yang jarang, cacar api dapat mengakibatkan kematian

Apakah saya berisiko untuk terkena cacar api?

Hampir setiap orang dewasa yang pernah menderita cacar air mempunyai risiko terkena cacar api. Risiko tersebut meningkat seiring bertambahnya usia. Hal ini terutama jika anda berusia lebih dari 50 tahun. Diperkirakan pada populasi umum, risiko seumur hidup untuk seseorang terkena cacar api sebesar 30 %. Untuk orang yang berusia 85 tahun keatas, 1 dari 2 orang akan memiliki cacar api.

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Apa yang harus saya ketahui sebelum menerima ZOSTAVAX?

Siapa yang seharusnya tidak menerima ZOSTAVAX?

Anda seharusnya tidak menerima ZOSTAVAX jika anda:

- Alergi terhadap salah satu komponenya (termasuk alergi terhadap gelatin dan neomycin)
- Memiliki defisiensi sistem imun akibat dari suatu penyakit, obat-obatan, atau pengobatan lain
- Memiliki TB (tuberkulosis) aktif yang tidak diobati
- Hamil

Apa yang harus saya katakan ke dokter saya sebelum menerima ZOSTAVAX?

Beritahu dokter anda, jika anda:

- Memiliki atau pernah memiliki masalah kesehatan
- Sedang menjalani atau pernah menjalani pengobatan yang dapat menurunkan sistem imun
- Memiliki alergi termasuk alergi terhadap gelatin atau neomycin.
- Mengalami demam
- Memiliki infeksi HIV

BADAN POM
RENEWAL
PERUBAHAN :
- kem porcine
- alamat pemohon
PARAF /TGL : 15/10/13

Pemakaian saat kehamilan

ZOSTAVAX tidak seharusnya diberikan kepada wanita hamil. Wanita dengan usia subur harus mencegah rencana kehamilan selama 3 bulan setelah mendapat vaksinasi.

Pemakaian saat menyusui

Beritahu dokter atau tenaga kesehatan anda jika anda sedang menyusui atau berencana akan menyusui. Dokter atau tenaga kesehatan anda akan memutuskan

apakah anda harus mendapat vaksinasi ZOSTAVAX atau tidak.

Dapatkah saya mengemudi atau mengoperasikan mesin sesaat setelah mendapatkan vaksinasi dengan ZOSTAVAX?

Tidak ada informasi yang menyatakan bahwa ZOSTAVAX memberikan efek terhadap kemampuan berkendara atau mengoperasikan mesin.

Apa yang harus saya ketahui tentang bahan tambahan lain dalam ZOSTAVAX?

Beritahu dokter anda jika pernah memiliki reaksi alergi oleh bahan yang ada dalam vaksin sebelum anda melakukan vaksinasi.

Bisakah saya melakukan vaksinasi dengan ZOSTAVAX bersama dengan vaksin lain?

ZOSTAVAX dapat diberikan bersamaan dengan vaksin influenza tidak inaktif.

ZOSTAVAX tidak boleh diberikan bersamaan dengan vaksin PNEUMOVAX 23. Untuk informasi lebih lanjut, bicarakan dengan dokter atau tenaga kesehatan anda karena lebih baik jika diberi jeda 4 minggu untuk mendapat vaksin lain.

BADAN POM
RENEWAL
PERUBAHAN :
- isi
- alamat pemasar
PARAF / TGL : 15/10/18

Bagaimana ZOSTAVAX diberikan?

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Zoster Vaccine Live (Oka/Merck)

ZOSTAVAX diberikan sebagai dosis tunggal dengan injeksi di bawah kulit.

ZOSTAVAX dapat diberikan bersamaan dengan vaksin influenza inaktif.

Apa saja efek yang tidak diinginkan yang dimiliki oleh ZOSTAVAX?

Sama seperti vaksin lainnya, ZOSTAVAX dapat memiliki efek samping. Pada beberapa studi, efek samping yang sering terjadi dilaporkan terjadi di tempat injeksi. Efek samping ini dapat berupa, kemerahan, nyeri, bengkak, benjolan keras, gatal, hangat, memar pada daerah injeksi. Dilaporkan juga sakit kepala dan nyeri pada lengan dan kaki.

Beberapa efek samping tambahan juga dilaporkan untuk ZOSTAVAX:

- Reaksi alergi, dapat menjadi serius dan juga terjadi kesulitan bernapas atau bengkak. Jika anda mengalami reaksi alergi, beritahu dokter anda segera.
- Cacar air
- Demam
- Gatal pada area injeksi
- Nyeri sendi
- Nyeri otot
- Mual
- Ruam
- Ruam pada area injeksi
- Cacar api
- Pembengkakan kelenjar di dekat area injeksi (dapat bertahan selama beberapa hari atau beberapa minggu)
- Guillain-Barré syndrome (kelemahan pada otot, sensasi abnormal, rasa menggelitik pada daerah lengan, kaki dan bagian atas tubuh)
- Penurunan kemampuan gerakan otot wajah

BADAN POM
RENEWAL
KETERANGAN :
PARAF / TGL :

Untuk daftar lengkap efek samping, tanyakan pada tenaga kesehatan anda.

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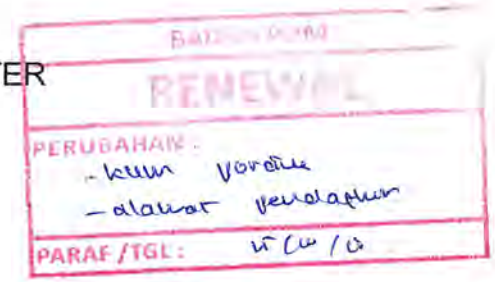
Beritahu dokter anda dengan segera jika terjadi gejala parah atau tidak biasa yang terjadi setelah anda menerima ZOSTAVAX. Jika keadaan berlanjut atau memburuk, cari bantuan medis.

Bagaimana mempelajari lebih lanjut tentang ZOSTAVAX dan kondisi apa yang diresepkan?:

Leaflet ini meringkas informasi tertentu tentang vaksin. Jika anda memiliki pertanyaan lain, tanyakan pada dokter atau tenaga kesehatan anda yang memiliki informasi lengkap tentang vaksin.



HARUS DENGAN RESEP DOKTER

Mengandung Babi

S-WPPI-V211-R-I-052018

PIL version 1.0