1. NAME OF THE MEDICINAL PRODUCT

ZOSTAVAX powder and solvent for suspension for injection
ZOSTAVAX powder and solvent for suspension for injection in a pre-filled syringe

shingles (herpes zoster) vaccine (live)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.65 mL) contains:

Varicella-zoster virus[1], Oka/Merck strain, (live, attenuated) not less than 19,400 PFU[2]
[1]produced in human diploid (MRC-5) cells
[2]PFU = Plaque-forming units

This vaccine may contain traces of neomycin. See sections 4.3 and 4.4.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection.

The powder is a white to off-white compact crystalline plug.
The solvent is a clear, colourless fluid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZOSTAVAX is indicated for prevention of herpes zoster ("zoster" or shingles) and herpes zoster-related post-herpetic neuralgia (PHN).

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

4.2 Posology and method of administration

Posology

Individuals should receive a single dose (0.65 mL).

The need for a booster dose is not known. See sections 4.8 and 5.1.

Paediatric population

The safety and efficacy of ZOSTAVAX in children and adolescents have not been established. No data are available.

There is no relevant use of ZOSTAVAX in children and adolescents for prevention of primary varicella infection (chickenpox).

Method of administration

The vaccine can be injected subcutaneously (SC) or intramuscularly (IM), preferably in the deltoid region (see sections 4.8 and 5.1).

The vaccine should be administered subcutaneously in patients with severe thrombocytopenia or any coagulation disorder (see section 4.4).

The vaccine should under no circumstances be injected intravascularly.

For precautions to be taken before handling or administering the medicinal product see section 6.6.

For instructions on reconstitution of the medicinal product before administration see section 6.6.

4.3 Contraindications

- History of hypersensitivity to the active substance, to any of the excipients or trace residuals (e.g. neomycin) (see sections 4.4 and 6.1).
- 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 4.4, 4.8 and 5.1); cellular immune deficiencies.
- Immunosuppressive therapy (including high-dose corticosteroids) (see sections 4.4 and 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 (see sections 4.8 and 5.1).
- Active untreated tuberculosis.
- Pregnancy. Furthermore, pregnancy should be avoided for 1 month following vaccination (see section 4.6).

4.4 Special warnings and precautions for use

Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic/anaphylactoid reaction following the administration of the vaccine, as there is a possibility of hypersensitivity reactions, not only to the active substances, but also to the excipients and trace residuals (e.g. neomycin) present in the vaccine (see sections 4.3, 4.8 and 6.1).

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. Patients who previously received immune suppressive therapy should be carefully evaluated for the reconstitution of the immune system prior to receiving Zostavax (see section 4.3).

The safety and efficacy of ZOSTAVAX have not been established in adults who are known to be infected with HIV with or without evidence of immunosuppression (see section 4.3) however, a phase II safety and immunogenicity study in HIV-infected adults with conserved immune function (CD 4+T cell count $\geq$ 200 cells/µL) has been completed (see sections 4.8 and 5.1).

This vaccine should be given subcutaneously to individuals with severe thrombocytopenia or any coagulation disorder, because these individuals may bleed following intramuscular injections.

ZOSTAVAX is not indicated for treatment of zoster or PHN.

Immunisation should be postponed in individuals suffering from moderate to severe acute febrile illness or infection.

As for any vaccine, vaccination with ZOSTAVAX may not result in protection in all vaccine recipients. See section 5.1.

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 [for example, varicella-zoster virus (VZV) susceptible infant grandchildren]. 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 from a vaccinee to a susceptible contact should be weighed against the risk of developing natural zoster and potentially transmitting wild-type VZV to a susceptible contact.

4.5 Interaction with other medicinal products and other forms of interaction

ZOSTAVAX can be administered concomitantly with inactivated influenza vaccine as separate injections and at different body sites (see section 5.1).

The concomitant use of ZOSTAVAX and a 23-valent pneumococcal polysaccharide vaccine resulted in reduced immunogenicity of ZOSTAVAX in a small clinical trial. However, data collected in a large observational study did not indicate increased risk for developing herpes zoster after concomitant administration of the two vaccines.

No data are currently available regarding concomitant use with other vaccines.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data on the use of ZOSTAVAX in pregnant women. Traditional non-clinical studies are insufficient with respect to reproductive toxicity (see section 5.3). However naturally-occurring varicella-zoster virus infection is known to sometimes cause foetal harm. ZOSTAVAX is not recommended to be administered to pregnant women. In any case, pregnancy should be avoided for one month following vaccination (see section 4.3).

Breast-feeding
It is unknown whether VZV is secreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to not administer ZOSTAVAX taking into account the benefit of breast-feeding for the child and the benefit of vaccination for the woman.

Fertility
ZOSTAVAX has not been evaluated in fertility studies.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. However, ZOSTAVAX is expected to have no or negligible influence on ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The most common adverse reactions reported in pivotal clinical trials were injection-site reactions. Headache and pain in the extremity were the most common systemic adverse reactions. Most of these local and systemic adverse reactions were reported as mild in intensity. Vaccine-related serious adverse reactions were reported for 0.01% subjects vaccinated with ZOSTAVAX and subjects who received placebo.

Data from a clinical trial (n=368) demonstrated that the current refrigerated formulation has a safety profile comparable to that of the frozen formulation.

b. Tabulated summary of adverse events

In clinical trials, general safety has been evaluated in more than 57,000 adults vaccinated with ZOSTAVAX.
Table 1 presents vaccine-related injection-site and systemic adverse reactions reported at a significantly greater incidence in the vaccine group versus the placebo group within 42 days post-vaccination in the ZOSTAVAX Efficacy and Safety trial (ZEST) study and in the Adverse Event Monitoring Substudy of Shingles Prevention Study (SPS).

Additional adverse reactions, spontaneously reported through post-marketing surveillance, are also included in Table 1. As these events are reported voluntarily from a population of uncertain size, it is not possible to reliably calculate their frequency or establish a causal relationship to vaccine exposure. Consequently, the frequencies of these adverse reactions have been estimated based on the adverse events reported in SPS and ZEST (regardless of vaccine relationship assigned by the investigator).

The adverse reactions are assigned frequency categories using the following convention:
Very Common (≥1/10);
Common (≥1/100 to <1/10);
Uncommon (≥1/1,000 to <1/100);
Rare (≥1/10,000 to <1/1,000);
Very rare (<1/10,000)

Table 1: Adverse Reactions from Clinical Trial Experience and Post-Marketing Surveillance

MedDRA System Organ Class	Adverse reaction terms	Frequency
Infections and infestations	Varicella, Herpes zoster (vaccine strain)	Very rare
Blood and lymphatic system disorders	Lymphadenopathy (cervical, axillary)	Uncommon
Immune system disorders	Hypersensitivity reactions including anaphylactic reactions	Rare
Nervous system disorders	Headache[1]	Common
Eye Disorders	Necrotizing retinitis (patients on immunosuppressive therapy)	Very rare
Gastrointestinal disorders	Nausea	Uncommon
Skin and subcutaneous tissue disorders	Rash	Common
Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia, Pain in extremity[1]	Common
General disorders and administration site conditions	Injection site: Erythema [1,2], Pain/tenderness[1,2], Pruritus[1,2], Swelling[1,2]	Very common
	Injection site: Induration[1], Haematoma[1], Warmth[1], Rash, Pyrexia	Common
	Injection site urticaria	Rare

[1] Clinical trials experience.
[2] Solicited adverse reaction within 5 days post-vaccination.

c. Description of selected adverse reactions

Injection site reactions
Vaccine-related injection-site adverse reactions were significantly greater for subjects vaccinated with ZOSTAVAX versus subjects who received placebo. In SPS, the overall incidence of vaccine-related injection-site adverse reactions were 48% for ZOSTAVAX and 17% for placebo in subjects 60 years of age and older.

In ZEST, the overall incidence of vaccine-related injection site adverse reactions were 63.9% for ZOSTAVAX and 14.4% for placebo in subjects 50 to 59 years of age. Most of these adverse reactions were reported as mild in intensity.

In other clinical trials evaluating ZOSTAVAX in subjects 50 years of age or older, including a study of concomitantly administered inactivated influenza vaccine, 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 (see section 5.1).

ZOSTAVAX was administered either subcutaneously (SC) or intramuscularly (IM) in subjects 50 years of age or older (see section 5.1). The general safety profiles of the SC and IM routes were otherwise comparable, but injection-site adverse reactions were significantly less frequent in the IM group (34%) compared with the SC group (64%).

Herpes zoster/herpes zoster-like rashes and Varicella/varicella-like rashes in clinical trials
In clinical trials the number of herpes zoster/herpes zoster-like rashes within the 42-day post-vaccination was low in both ZOSTAVAX and placebo groups. The majority of rashes have been rated as mild to moderate; no complications from rash have been observed in the clinical setting. Most of the reporting rashes that were VZV positive by PCR analysis were associated with wild-type VZV.

In SPS and ZEST, the number of subjects who reported herpes zoster/herpes zoster-like rashes was less than 0.2% for ZOSTAVAX and placebo groups, with no significant difference observed between the two groups. The number of subjects who reported varicella/varicella-like rashes was less than 0.7% for ZOSTAVAX and placebo.

The Oka/Merck strain of VZV was not detected from any specimens in SPS or ZEST. VZV was detected in one (0.01%) specimen from a ZOSTAVAX recipient reporting a varicella/varicella-like rash; however, the virus strain (wild type or Oka/Merck strain) could not be determined. Across all other clinical trials, the Oka/Merck strain was identified by PCR analysis from the lesion specimens of only two subjects who reported varicella-like rashes (onset on Day 8 and 17).

d. Special populations

Adults with a history of herpes zoster (HZ) prior to vaccination
ZOSTAVAX was administered to subjects 50 years of age or older with a history of herpes zoster (HZ) prior to vaccination (see section 5.1). The safety profile was generally similar to that seen in the Adverse Event Monitoring Substudy of the SPS.

Adults on chronic/maintenance systemic corticosteroids
In 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, the safety profile was generally comparable to that seen in the Adverse Event Monitoring Substudy of the SPS (see sections 4.3 and 5.1).

HIV-infected adults with conserved immune function
In a clinical trial, ZOSTAVAX was administered to HIV-infected adults (18 years of age or older, CD4+ T cell count $\geq$ 200 cells/µL) (see section 5.1). The safety profile was generally similar to the Adverse Event Monitoring Substudy of the SPS. Adverse events were followed up to Day 42 post vaccination and serious adverse events throughout the entire study period (i.e. through Day 180). Of the 295 ZOSTAVAX recipients, one case of serious vaccine related maculo-papular rash was reported on Day 4 following Dose 1 of ZOSTAVAX (see section 4.3).

VZV-seronegative adults
Based on limited data from 2 clinical trials that enrolled VZV-seronegative or low seropositive subjects (30 years of age or older) receiving live attenuated zoster vaccine, injection site and systemic adverse experiences were generally similar to those reported by other subjects who received ZOSTAVAX in clinical trials, with 2 of the 27 subjects reporting fever. No subjects reported varicella-like or herpes zoster-like rashes. No serious vaccine-related adverse experiences were reported.

e. Other studies

Adults receiving additional doses/revaccination
In a clinical study, adults 60 years of age or older received a second dose of ZOSTAVAX 42 days following the initial dose (see section 5.1). The frequency of vaccine-related adverse experiences after the second dose of ZOSTAVAX was generally similar to that seen with the first dose.

In another study, ZOSTAVAX was administered as a booster dose to HZ history-negative subjects 70 years of age or older who had received a first dose approximately 10 years previously, and as a first dose to HZ history-negative subjects 70 years of age or older (see section 5.1). The frequency of vaccine-related adverse experiences after the booster dose of ZOSTAVAX was generally similar to that seen with the first dose.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance,

Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Administration of a higher than recommended dose of ZOSTAVAX was reported rarely and the adverse reaction profile was comparable to that observed with the recommended dose of ZOSTAVAX.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Viral Vaccine; ATC code: J07BK02

Mechanism of action
Anyone who has been infected with VZV, including those without a clinical history of varicella, is at risk for developing zoster. This risk 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
The protective clinical efficacy of ZOSTAVAX was demonstrated in two large, randomised, placebo controlled clinical trials where subjects received ZOSTAVAX subcutaneously (see Tables 2 and 3).

ZOSTAVAX Efficacy and Safety Trial (ZEST) in subjects 50 to 59 years of age:
The ZEST study was a placebo-controlled, double-blind clinical trial in which 22,439 subjects were randomised to receive a single dose of either ZOSTAVAX or placebo and were followed for the development of zoster for a median of 1.3 years (range 0 to 2 years). 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 to placebo (see Table 2).

Table 2: Efficacy of ZOSTAVAX on zoster incidence compared with placebo in the ZEST trial in subjects 50 to 59 years of age*

ZOSTAVAX			**Placebo**			**Vaccine efficacy (95% CI)**
Number of subjects	Number of zoster cases	Incidence rate of zoster per 1,000 person years	Number of subjects	Number of zoster cases	Incidence rate of zoster per 1,000 person years	
11,211	30	2.0	11,228	99	6.6	70% (54%, 81%)

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

Shingles Prevention Study (SPS) in Subjects 60 years of age and older:
The SPS study was a placebo-controlled, double-blind clinical trial in which 38,546 subjects were randomised to receive a single dose of either ZOSTAVAX or placebo and were followed for the development of zoster for a median of 3.1 years (range 31 days to 4.9 years).

ZOSTAVAX significantly decreased the incidence of zoster compared with placebo (see Table 3).

Table 3: Efficacy of ZOSTAVAX on zoster incidence compared with placebo in the SPS in subjects 60 years of age and older*

Age group†	**ZOSTAVAX**			**Placebo**			**Vaccine efficacy (95% CI)**
	Number of subjects	Number of zoster cases	Incidence rate of zoster per 1,000 person years	Number of subjects	Number of zoster cases	Incidence rate of zoster per 1,000 person years	
≥ 60	19,254	315	5.4	19,247	642	11.1	51% (44%, 58%)
60-69	10,370	122	3.9	10,356	334	10.8	64% (56%, 71%)
≥ 70	8,884	193	7.2	8,891	308	11.5	38% (25%, 48%)
70-79	7,621	156	6.7	7,559	261	11.4	41% (28%, 52%)

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

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

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 significantly decreased the incidence of Post-herpetic Neuralgia (PHN) compared with placebo (see Table 4). In subjects who developed zoster, ZOSTAVAX decreased the risk of subsequently developing PHN. In the vaccine group, the risk of developing PHN after zoster was 9 % (27/315), while in the placebo group it was 13 % (80/642). This effect was more prominent in the group of older subjects (≥70 years of age), where the risk of developing PHN after zoster was reduced to 10% in the vaccine group vs. 19% for the placebo group.

Table 4: Efficacy of ZOSTAVAX on PHN† incidence compared with placebo in the SPS in subjects 60 years of age and older*

Age group‡	ZOSTAVAX			Placebo			Vaccine efficacy (95% CI)
	Number of subjects	Number of PHN cases	Incidence rate of PHN per 1,000 person years	Number of subjects	Number of PHN cases	Incidence rate of PHN per 1,000 person years	
≥ 60	19,254	27	0.5	19,247	80	1.4	67%§ (48%, 79%)
60-69	10,370	8	0.3	10,356	23	0.7	66% (20%, 87%)
≥ 70	8,884	19	0.7	8,891	57	2.1	67% (43%, 81%)
70-79	7,621	12	0.5	7,559	45	2.0	74% (49%, 87%)

† PHN was defined as zoster-associated pain rated as ≥3 (on a 0-10 scale), persisting or appearing more than 90 days after onset of zoster rash using Zoster Brief Pain Inventory (ZBPI).
* The table is based on the Modified Intent-To-Treat (MITT) population that included all subjects randomised in the study who were followed for at least 30 days post-vaccination and did not develop an evaluable case of zoster within the first 30 days post-vaccination.
‡ Age strata at randomisation were 60-69 and ≥70 years of age.
§ Age-adjusted estimate based on the age strata (60-69 and ≥70 years of age) at randomisation.

ZOSTAVAX significantly reduced the zoster pain Burden of Illness (BOI) score (see Table 5).

Table 5: Reduction of the zoster-associated pain by the BOI† score in the SPS in subjects 60 years of age and older

Age group‡	ZOSTAVAX			Placebo			Vaccine efficacy (95% CI)
	Number of subjects	Number of zoster confirmed cases	Mean BOI score	Number of subjects	Number of zoster confirmed cases	Mean BOI score	
≥ 60	19,254	315	2.21	19,247	642	5.68	61% (51%, 69%)
60-69	10,370	122	1.5	10,356	334	4.33	66% (52%, 76%)
≥ 70	8,884	193	3.47	8,891	308	7.78	55% (40%, 67%)
70-79	7,621	156	3.04	7,559	261	7.43	59% (43%, 71%)

† The zoster 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.
‡ Age strata at randomisation were 60-69 and ≥70 years of age.

Prevention of HZ cases with severe pain in the entire SPS study population
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 (11 vs. 40 cases, respectively).

Reduction of zoster pain severity-by-duration in vaccinated individuals who developed zoster
With regard to the acute pain (pain between 0-30 days) there was no statistically significant difference between the vaccine group and the placebo group.

However, among vaccinated individuals who developed PHN, ZOSTAVAX significantly reduced PHN-associated (chronic) 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).

Overall, among vaccinated individuals who developed zoster, ZOSTAVAX significantly reduced overall acute and chronic zoster-associated pain compared with placebo. Over the 6-month (acute and chronic) follow-up period, there was a 22% reduction (p =0.008) in the severity-by-duration score and a 52% (95% CI: [7 to 74%]) reduction (from 6.2% to 3.5%) in the risk of having zoster with severe and long-lasting pain (severity-by-duration score of >600).

Zostavax persistence of protection

The persistence of protection following vaccination has been evaluated through longer-term follow-up in Short-term Persistence Substudy (STPS) and Long-term Persistence Substudy (LTPS) and supports the continued benefit of ZOSTAVAX throughout the follow-up periods studied. The STPS was initiated to accrue additional information on the persistence of vaccine efficacy for subjects who received ZOSTAVAX in SPS.

Persistence of ZOSTAVAX efficacy was studied 4 to 7 years post-vaccination in the STPS, which included 7,320 subjects previously vaccinated with ZOSTAVAX and 6,950 subjects previously vaccinated with placebo in the SPS (mean age at enrollment was 73.3 years); and 7 to 10 years post-vaccination in the Long-term Persistence Substudy (LTPS), which included 6,867 subjects previously vaccinated with ZOSTAVAX (mean age at enrollment into the LTPS was 74.5 years). The median follow-up was ~1.2 years (range is one day to 2.2 years) and ~3.9 years (range is one week to 4.75 years) in STPS and LTPS, respectively. During the course of the STPS, placebo recipients were offered ZOSTAVAX, at which time they were considered to have completed the STPS. A concurrent placebo control was not available in the LTPS; data from prior placebo recipients were used to estimate vaccine efficacy.

In the STPS, there were 84 evaluable zoster cases [8.4/1,000 person-years] in the ZOSTAVAX group and 95 evaluable cases [14.0/1,000 person-years] in the placebo group. The estimated vaccine efficacy during the STPS follow-up period was 40% (95% CI: [18 to 56%]) for zoster incidence, 60% (95% CI: [-10 to 87%]) for PHN incidence and 50% (95% CI: [14 to 71%]) for zoster BOI.

In the LTPS, there were 263 evaluable zoster cases reported among 261 patients [10.3/1000 person-years]. The estimated vaccine efficacy during the LTPS follow-up period was 21% (95% CI: [11 to 30%]) for zoster incidence, 35% (95% CI: [9 to 56%]) for PHN incidence and 37% (95% CI: [27 to 46%]) for zoster BOI.

Long-term effectiveness study in individuals 50 years of age or older

In a large-scale ongoing US prospective observational cohort study of the long-term effectiveness of ZOSTAVAX, individuals 50 years of age or older at the time of vaccination are being followed for the occurrence of HZ and PHN using validated endpoints.

In an interim analysis of 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. The results showed that ZOSTAVAX is effective in reducing HZ and PHN incidence in vaccinated individuals as compared to an unvaccinated reference group.

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 6).

Table 6: 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)	¶
5-year postvaccination	¶	49% (47, 52)	46% (43, 48)	44% (38, 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
Abbreviations: VE denotes vaccine effectiveness; CI confidence interval; DxCG diagnostic cost group; HCUP healthcare cost and utilization project

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 7).

Table 7: 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	98% (-∞, 100)	74% (66, 80)	73% (65, 79)	63% (49, 73)	¶
5-year postvaccination	¶	72% (65, 77)	69% (62, 75)	61% (47, 71)	¶

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

Immunogenicity of ZOSTAVAX

Shingles Prevention Study (SPS)

Within SPS, immune responses to vaccination were evaluated in a subset of the enrolled subjects (N=1395). ZOSTAVAX elicited significantly higher VZV-specific immune responses at 6 weeks post-vaccination compared with placebo.

ZOSTAVAX Efficacy and Safety Trial (ZEST)

Within 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 significantly higher VZV-specific immune responses at 6 weeks post-vaccination compared with placebo.

When evaluated at 4 weeks post-vaccination, the immunogenicity of the current refrigerator-stable formulation was shown to be similar to the immunogenicity of the earlier frozen formulation of ZOSTAVAX.

Subjects who received ZOSTAVAX by SC (subcutaneous) or IM (intramuscular) route

In an open-label, randomised, controlled clinical trial, ZOSTAVAX was administered either by SC route or by IM route to 353 subjects 50 years of age or older. Subjects with severe thrombocytopenia or any other coagulation disorder were excluded. The VZV specific immune responses to ZOSTAVAX at Week 4 post-vaccination were comparable whether administered by SC or IM route.

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 nonconcomitantly (N=380) with inactivated split influenza vaccine. The VZV-specific immune responses to both vaccines at 4 weeks post-vaccination were similar, whether administered concomitantly or nonconcomitantly.

In a double-blind, controlled clinical trial, 473 adults, 60 years of age or older, were randomised to receive a single dose of ZOSTAVAX either concomitantly (N=237), or nonconcomitantly (N=236) with 23-valent pneumococcal polysaccharide vaccine. At four weeks post-vaccination, the VZV-specific immune responses following concomitant use were not similar to the VZV-specific immune responses following nonconcomitant administration. However in a US effectiveness cohort study of 35,025 adults ≥ 60 years old, no increased risk of herpes zoster was observed in individuals who received ZOSTAVAX and 23-valent pneumococcal polysaccharide vaccine concomitantly (n=16,532) as compared to individuals receiving ZOSTAVAX one month to one year after 23-valent pneumococcal polysaccharide vaccine (n=18,493) in routine practice. The adjusted hazard ratio comparing the incidence rate of HZ in the two groups was 1.04 (95% CI, 0.92, 1.16) over a median follow-up of 4.7 years. The data do not indicate that concomitant administration alters the effectiveness of ZOSTAVAX.

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 prior to vaccination to assess immunogenicity and safety (see section 4.8) of ZOSTAVAX. ZOSTAVAX induced a significantly higher VZV-specific immune response at 4 weeks post-vaccination, compared with placebo.

VZV-specific immune responses were generally similar in subjects 50 to 59 compared to subjects ≥60 years of age.

Adults receiving additional doses/revaccination
The need for, or timing of, a booster dose with ZOSTAVAX has not yet been determined. In an open-label study, ZOSTAVAX was administered as: (1) a booster dose to 201 zoster history-negative subjects 70 years of age or older who had received a first dose approximately 10 years previously as participants in the SPS, and (2) a first dose to 199 zoster history-negative subjects 70 years of age or older. The VZV-specific immune responses to vaccine 6 weeks post-vaccination was comparable in the booster dose and first dose group.

Subjects on chronic/maintenance systemic corticosteroids
In a double-blind, placebo-controlled, randomised 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 immune response at 6 weeks post-vaccination.

HIV-infected adults with conserved immune function
In a double-blind, placebo-controlled randomised clinical trial, ZOSTAVAX was administered to HIV-infected adults (18 years of age or older; median age 49 years) on appropriate antiretroviral therapy with conserved immune function (CD4+ T cell count ≥ 200 cells/μL). Although, ZOSTAVAX is indicated as a single dose regimen (see section 4.2), a two-dose regimen was used. 286 subjects received two doses and 9 subjects received only one dose. The VZV-specific immune responses following Doses 1 and 2 were similar (see section 4.3).

Immunocompromised subjects
The vaccine has not been studied in subjects with impaired immunity.

The European Medicines Agency has waived the obligation to submit the results of studies with ZOSTAVAX in all the subsets of paediatric population (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sucrose
Hydrolysed gelatin
Sodium chloride
Potassium dihydrogen phosphate
Potassium chloride
Monosodium L-glutamate monohydrate
Disodium phosphate

Sodium hydroxide (to adjust pH)
Urea

Solvent:
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

18 months.

After reconstitution, the vaccine should be used immediately. However, in-use stability has been demonstrated for 30 minutes when stored at 20 °C – 25 °C.

6.4 Special precautions for storage

Store and transport refrigerated (2 °C – 8 °C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

ZOSTAVAX with solvent for reconstitution supplied in a vial:
Powder in a vial (glass) with a stopper (butyl rubber) and flip off cap (aluminium) and solvent in a vial (glass) with a stopper (chlorobutyl rubber) and flip off cap (aluminium) in a pack size of 1 or 10.

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

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Avoid contact with disinfectants as they may inactivate the vaccine virus.

To reconstitute the vaccine, use the solvent provided. When reconstituted, ZOSTAVAX is a semi-hazy to translucent, off-white to pale yellow liquid.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of infectious agents from one individual to another.

Reconstitution instructions

ZOSTAVAX with solvent for reconstitution supplied in a vial:
Withdraw the entire contents of the solvent vial into a syringe.
Inject all the solvent into the vial of lyophilised vaccine.
Gently agitate to dissolve completely.
Withdraw the entire content of the reconstituted vaccine using the same syringe. Inject the vaccine.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.

ZOSTAVAX with solvent for reconstitution supplied in a pre-filled syringe:
If two needles are provided, separate needles should be used for the reconstitution and administration of the vaccine.
To reconstitute the vaccine, inject all the solvent in the pre-filled syringe into the vial of lyophilised vaccine and gently agitate to mix thoroughly.
Withdraw the entire contents of the reconstituted vaccine using the same syringe. Inject the vaccine.
One or 2 separate needles may be available in the secondary packaging of the presentation containing the pre-filled syringe without attached needle.
The needle should be pushed into the extremity of the syringe and rotated a quarter of a turn (90°) to secure the connection.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.

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.

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

7. MARKETING AUTHORISATION HOLDER

MSD VACCINS
162 avenue Jean Jaurès
69007 Lyon
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/341/001
EU/1/06/341/002
EU/1/06/341/003
EU/1/06/341/004
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EU/1/06/341/008
EU/1/06/341/009
EU/1/06/341/010
EU/1/06/341/011
EU/1/06/341/012
EU/1/06/341/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 May 2006
Date of latest renewal: 11 February 2016

10. DATE OF REVISION OF THE TEXT

29 November 2018

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.