Product Information as approved by the CHMP on 13 December 2012, pending endorsement by the European Commission

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZOSTAVAX powder and solvent for suspension for injection

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 19400 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.

Excipients with known effect:
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) administered subcutaneously.

The need for a second dose is currently unknown. See section 5.1.

Paediatric population

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

Method of administration

The vaccine is to be injected SUBCUTANEOUSLY, preferably in the deltoid region.

Do not inject intravascularly.

For precautions 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; cellular immune deficiencies.
- Immunosuppressive therapy (including high-dose corticosteroids); 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 not indicated for treatment of zoster or PHN.

Deferral of vaccination should be considered in the presence of fever.

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

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).

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, 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).

ZOSTAVAX and 23-valent pneumococcal polysaccharide vaccine should not be given concomitantly because concomitant use in a clinical trial resulted in reduced immunogenicity of ZOSTAVAX (see section 5.1).

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 studies in pregnant women. It is also not known whether ZOSTAVAX can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. However naturally-occurring varicella-zoster virus infection is known to sometimes cause foetal harm. As ZOSTAVAX is not indicated in individuals less than 50 years of age, ZOSTAVAX is not intended 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 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 breast-feeding 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

In clinical trials, ZOSTAVAX has been evaluated for general safety in more than 32000 adults.

Shingles Prevention Study (SPS) in Subjects 60 Years of Age and Older
In the largest of these trials, the Shingles Prevention Study (SPS), 38546 subjects received a single dose of either the frozen formulation of ZOSTAVAX (n=19270) or placebo (n=19276) and were monitored for safety throughout the study. During the study, vaccine-related serious adverse reactions 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=3345 received ZOSTAVAX and n=3271 received placebo) were provided vaccination report cards to record adverse events occurring from Days 0 to 42 post vaccination in addition to undergoing routine safety monitoring throughout the study.

The vaccine-related injection-site and systemic adverse reactions reported at a significantly greater incidence in the vaccine group versus the placebo group in the Adverse Event Monitoring Substudy are listed in Table 1. Most of these adverse reactions were reported as mild in intensity. Table 1 also includes additional adverse events which have been reported spontaneously through post-marketing surveillance.

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).

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

Within the 42-day postvaccination reporting period in the SPS, the number of reported 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.

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 vaccine-related injection-site and systemic adverse experiences reported in the ZEST study are presented in Table 1. Table 1 also includes additional adverse events which have been reported spontaneously through post-marketing surveillance.

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). Most of these adverse reactions were reported as mild in intensity.

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.

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 the 17 reported noninjection-site zosteriform and varicella-like rashes, 10 specimens were available and adequate for PCR testing. The Oka/Merck strain was identified by PCR analysis from the lesion specimens of only two subjects who reported varicella-like rashes (onset on Day 8 and 17).

In other 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 (see section 5.1).

Data from a clinical trial (n=368) demonstrated that the current refrigerated formulation is generally well tolerated with a safety profile comparable to that of the frozen formulation.

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

Based on limited data from 2 clinical trials that enrolled VZV-seronegative or low seropositive subjects (27 subjects 30 years of age or older received 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.

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX was administered to 206 subjects 60 years of age or older who were receiving chronic/maintenance systemic corticosteroid therapy at a daily dose equivalent of 5 to 20 mg of prednisone for at least 2 weeks prior to enrollment, and 6 weeks or more following vaccination to assess the immunogenicity and safety profile of ZOSTAVAX. In this clinical trial, the safety profile was generally comparable to that seen in the Adverse Event Monitoring Substudy of the SPS (see section 4.3 Contraindications regarding corticosteroids).

<u>b. Tabulated summary of adverse events</u>

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 in the Adverse Event Monitoring Substudy.

They are ranked under headings of frequency 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 also includes additional adverse events which have been reported spontaneously through post-marketing surveillance. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Consequently, the frequency of these adverse events is qualified as "*not known*".

Table 1

MedDRA System Organ Class	Adverse reactions	Frequency
Blood and lymphatic system disorders	Lymphadenopathy (cervical, axillary)	Not known**
Immune system disorders	Hypersensitivity reactions including anaphylactic reactions	Not known**
Nervous system disorders	Headache	Common
Gastrointestinal disorders	Nausea	Not known**
Skin and subcutaneous tissue disorders	Rash	Not known**
Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia Pain in extremity	Not known** Common
General disorders and administration site conditions	Erythema †*, Pain/tenderness †*, Swelling†*, Pruritus† Haematoma†, Warmth†, Induration† Rash †, Urticaria †, Pyrexia	Very common Common Not known**
Infections and infestations	Varicella	Very rare

*Several adverse reactions were solicited (within 5 days postvaccination).
** Post marketing adverse events (frequency cannot be estimated from the available data).
† Injection-site adverse reactions

4.9 Overdose

Administration of a higher than recommended dose of ZOSTAVAX was reported rarely and the adverse event 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).

Evaluation of Clinical Efficacy Afforded by ZOSTAVAX
Shingles Prevention Study (SPS) in Subjects 60 Years of Age and Older:
ZOSTAVAX significantly reduced the risk of developing zoster and PHN compared with placebo. In addition, ZOSTAVAX significantly reduced zoster-associated pain as measured by the HZ pain Burden of Illness (BOI) score (see results and definition in Table 2).

Table 2
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%

*Vaccine efficacy = relative reduction in the endpoint measurement in the vaccine group compared with the placebo group
**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.

In the Shingles Prevention Study (SPS), a placebo-controlled, double-blind clinical trial of ZOSTAVAX, 38546 subjects 60 years of age or older were randomized to receive a single dose of either ZOSTAVAX (n=19270) or placebo (n=19276).

ZOSTAVAX significantly decreased the incidence of zoster compared with placebo (315 [5.4/1000 person-years] vs. 642 cases [11.1/1000 person-years], respectively; p<0.001). The protective efficacy of ZOSTAVAX against zoster was 51% (95% CI: [44 to 58%]). ZOSTAVAX reduced the incidence of zoster by 64% (95% CI: [56 to 71%]) in individuals 60-69 years of age and by 38% (95% CI: [25 to 48%]) in individuals ≥70 years of age.

In the SPS, the reduction in zoster was seen in almost all dermatomes. Ophthalmic zoster occurred in 35 subjects vaccinated with ZOSTAVAX vs. 69 subjects who received placebo. Impaired vision occurred in 2 subjects vaccinated with ZOSTAVAX vs. 9 who received placebo.

ZOSTAVAX decreased the incidence of PHN compared with placebo [(27 cases [0.5/1000 person-years] vs. 80 cases [1.4/1000 person-years], respectively; p<0.001). In this trial, the definition of PHN was clinically significant zoster-associated pain persisting or appearing at least 90 days after the onset of rash. The protective efficacy of ZOSTAVAX against PHN was 67% (95% CI: [48 to 79%]). Referring only to subjects who developed zoster, there was a decrease in 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.

ZOSTAVAX reduced the HZ pain BOI score by approximately 61% (95% CI: [51 to 69%]), compared with placebo. The effect was more pronounced in the younger age group (60 to 69 years) where the efficacy of ZOSTAVAX on HZ pain BOI was 66% compared to 55% in patients ≥70 years of age; however, this difference was not statistically significant (p=0.266).

Prevention of HZ cases with severe pain in the entire 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. The HZ pain severity-by-duration score was 89 (95%CI: [82 to 97%]) for the vaccine group vs. 92 (95% CI: [87 to 97%]) for the placebo group. The overall use of analgesic medication was similar in both study groups.

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).

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 HZ with severe and long-lasting pain (severity-by-duration score of >600).

The Short-term Persistence Substudy (STPS):
The STPS was initiated to accrue additional information on the persistence of vaccine efficacy and to preserve a subset of subjects from the SPS for the long-term persistence substudy (LTPS). The STPS included 7,320 subjects previously vaccinated with ZOSTAVAX and 6,950 subjects previously vaccinated with placebo in the SPS. The mean age at enrollment in the STPS was 73.3 years. During the course of the STPS, placebo recipients were offered ZOSTAVAX, at which time they were considered to have completed the STPS.

The STPS analyses for vaccine efficacy are based on data collected primarily 4 to 7 years postvaccination in the SPS. The median follow-up in the STPS was ~1.2 years (range is one day to 2.2 years). In the STPS, there were 84 evaluable HZ cases [8.4/1000 person-years] in the ZOSTAVAX group and 95 evaluable cases [14.0/1000 person-years] in the placebo group.-The estimated vaccine efficacy during the STPS follow-up period was 40% (95% CI: [18 to 56%]) for HZ incidence, 60% (95% CI: [-10 to 87%]) for PHN incidence and 50% (95% CI: [14 to 71%]) for HZ BOI.

The Long-term Persistence Substudy (LTPS):
Following completion of the STPS, the LTPS evaluated the duration of protection against HZ, PHN and HZ BOI in a total of 6,867 subjects previously vaccinated with ZOSTAVAX in the SPS. The mean age at enrollment into the LTPS was 74.5 years. A concurrent placebo control was not available in the LTPS; data from prior placebo recipients were used to estimate vaccine efficacy.

The LTPS analyses for vaccine efficacy are based on data collected primarily from Year 7 through Year 10 following vaccination in the SPS. The median follow-up during the LTPS was ~3.9 years (range is one week to 4.75 years). There were 263 evaluable HZ cases reported among 261 patients [10.3/1000 person-years] during the LTPS. The estimated vaccine efficacy during the LTPS follow-up period was 21% (95% CI: [11 to 30%]) for HZ incidence, 35% (95% CI: [9 to 56%]) for PHN incidence and 37% (95% CI: [27 to 46%]) for HZ BOI.

ZOSTAVAX Efficacy and Safety Trial (ZEST) in Subjects 50 to 59 Years of Age:
The ZOSTAVAX Efficacy and Safety Trial (ZEST) was 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 70% (95% CI: [54 to 81%]).

<u>Immunogenicity of ZOSTAVAX</u>

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/10^6 PBMCs], p<0.001) were demonstrated. When evaluated at 4 weeks postvaccination, the immunogenicity of the current refrigerator-stable formulation was shown to be similar to the immunogenicity of the earlier frozen formulation 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).

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 split influenza vaccine. The antibody responses to both vaccines at 4 weeks postvaccination were similar, whether administered concomitantly or nonconcomitantly.

In a double-blind, controlled clinical trial, 473 adults, 60 years of age or older, were randomized to receive a single dose of ZOSTAVAX either concomitantly (N=237), or nonconcomitantly with 23-valent pneumococcal polysaccharide vaccine (N=236). At four weeks postvaccination, the VZV antibody levels following concomitant use were not similar to 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])). VZV antibody levels 4 weeks postvaccination were increased 1.9-fold (95% CI: [1.7, 2.1]; meeting the pre-specified acceptance criterion) in the concomitant group vs. 3.1-fold (95% CI: [2.8, 3.5]) in the nonconcomitant group. The GMTs for 23-valent pneumococcal polysaccharide vaccine antigens were similar between the two groups. There was no significant difference in the safety profile between concomitant and nonconcomitant administration of ZOSTAVAX and 23-valent pneumococcal polysaccharide vaccine, except for headache and pneumococcal vaccine injection site erythema and swelling, which were more common in the concomitant group.

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 and safety (see section 4.8) of ZOSTAVAX. ZOSTAVAX induced a significantly higher VZV-specific immune response measured by gpELISA at 4 weeks postvaccination, compared with placebo (2.1-fold difference (95% CI: [1.5 to 2.9]), p<0.001, GMT of 812 vs. 393 gpELISA units/ml). VZV antibody responses were generally similar in subjects 50 to 59 compared to subjects ≥60 years of age.

Immunogenicity in subjects on chronic/maintenance systemic corticosteroids

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX was administered to 206 subjects 60 years of age or older who were receiving chronic/maintenance systemic corticosteroid therapy at a daily dose equivalent of 5 to 20 mg of prednisone for at least 2 weeks prior to enrollment, and 6 weeks or more following vaccination to assess the immunogenicity and safety profile of ZOSTAVAX. Compared with placebo, ZOSTAVAX induced a higher VZV-specific gpELISA antibody GMT at 6 weeks postvaccination (GMT of 531.1 vs. 224.3 gpELISA units/ml, respectively). The Geometric mean

fold-rise of immune response following vaccination as measured by gpELISA was 2.3-fold (95% CI: [2.0 to 2.7]) compared to 1.1-fold (95% CI: [1.0 to 1.2]) in the placebo group.

Revaccination
The need for, or timing of, revaccination with ZOSTAVAX has not yet been determined.

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.

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

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 SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sucrose
Hydrolysed gelatin
Sodium chloride
Potassium dihydrogen phosphate
Potassium chloride
Monosodium L-glutamate
Anhydrous 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 in the same syringe.

6.3 Shelf life

18 months.

After reconstitution, the vaccine should be used immediately. However, the 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 the reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Avoid contact with disinfectants.

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
Withdraw the entire contents of the solvent vial into a syringe.
Inject all the solvent into the vial of lyophilized vaccine.
Gently agitate to dissolve completely.
Withdraw the entire content of the reconstituted vaccine into a syringe for injection.

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 use the reconstituted vaccine if you notice any particulate matter or if the appearance of the solvent or of the reconstituted vaccine differs from that described above.

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

7. MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD, SNC
8, rue Jonas Salk
F-69007 Lyon
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/341/ 001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 May 2006
Date of latest renewal: 23 May 2011

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

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 19400 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.

Excipients with known effect:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection in a pre-filled syringe.

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) administered subcutaneously.

The need for a second dose is currently unknown. See section 5.1.

Paediatric population

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

Method of administration

The vaccine is to be injected SUBCUTANEOUSLY, preferably in the deltoid region.

Do not inject intravascularly.

For precautions 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; cellular immune deficiencies.
- Immunosuppressive therapy (including high-dose corticosteroids); 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 not indicated for treatment of zoster or PHN.

Deferral of vaccination should be considered in the presence of fever.

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

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).

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, 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).

ZOSTAVAX and 23-valent pneumococcal polysaccharide vaccine should not be given concomitantly because concomitant use in a clinical trial resulted in reduced immunogenicity of ZOSTAVAX (see section 5.1).

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 studies in pregnant women. It is also not known whether ZOSTAVAX can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. However naturally-occurring varicella-zoster virus infection is known to sometimes cause foetal harm. As ZOSTAVAX is not indicated in individuals less than 50 years of age, ZOSTAVAX is not intended 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 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 breast-feeding 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

In clinical trials, ZOSTAVAX has been evaluated for general safety in more than 32000 adults.

Shingles Prevention Study (SPS) in Subjects 60 Years of Age and Older
In the largest of these trials, the Shingles Prevention Study (SPS), 38546 subjects received a single dose of either the frozen formulation of ZOSTAVAX (n=19270) or placebo (n=19276) and were monitored for safety throughout the study. During the study, vaccine-related serious adverse reactions 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=3345 received ZOSTAVAX and n=3271 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 vaccine-related injection-site and systemic adverse reactions reported at a significantly greater incidence in the vaccine group versus the placebo group in the Adverse Event Monitoring Substudy are listed in Table 1. Most of these adverse reactions were reported as mild in intensity. Table 1 also includes additional adverse events which have been reported spontaneously through post-marketing surveillance.

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).

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

Within the 42-day postvaccination reporting period in the SPS, the number of reported 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.

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 vaccine-related injection-site and systemic adverse experiences reported in the ZEST study are presented in Table 1. Table 1 also includes additional adverse events which have been reported spontaneously through post-marketing surveillance.

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). Most of these adverse reactions were reported as mild in intensity.

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.

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 the 17 reported noninjection-site zosteriform and varicella-like rashes, 10 specimens were available and adequate for PCR testing. The Oka/Merck strain was identified by PCR analysis from the lesion specimens of only two subjects who reported varicella-like rashes (onset on Day 8 and 17).

In other 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 (see section 5.1).

Data from a clinical trial (n=368) demonstrated that the current refrigerated formulation is generally well tolerated with a safety profile comparable to that of the frozen formulation.

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

Based on limited data from 2 clinical trials that enrolled VZV-seronegative or low seropositive subjects (27 subjects 30 years of age or older received 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.

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX was administered to 206 subjects 60 years of age or older who were receiving chronic/maintenance systemic corticosteroid therapy at a daily dose equivalent of 5 to 20 mg of prednisone for at least 2 weeks prior to enrollment, and 6 weeks or more following vaccination to assess the immunogenicity and safety profile of ZOSTAVAX. In this clinical trial, the safety profile was generally comparable to that seen in the Adverse Event Monitoring Substudy of the SPS (see section 4.3 Contraindications regarding corticosteroids).

b. Tabulated summary of adverse events

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 in the Adverse Event Monitoring Substudy.

They are ranked under headings of frequency 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 also includes additional adverse events which have been reported spontaneously through post-marketing surveillance. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Consequently, the frequency of these adverse events is qualified as "*not known*".

Table 1

MedDRA System Organ Class	Adverse reactions	Frequency
Blood and lymphatic system disorders	Lymphadenopathy (cervical, axillary)	Not known**
Immune system disorders	Hypersensitivity reactions including anaphylactic reactions	Not known**
Nervous system disorders	Headache	Common
Gastrointestinal disorders	Nausea	Not known**
Skin and subcutaneous tissue disorders	Rash	Not known**
Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia Pain in extremity	Not known** Common
General disorders and administration site conditions	Erythema †*, Pain/tenderness †*, Swelling†*, Pruritus† Haematoma†, Warmth†, Induration† Rash †, Urticaria †, Pyrexia	Very common Common Not known**
Infections and infestations	Varicella	Very rare

*Several adverse reactions were solicited (within 5 days postvaccination).
** Post marketing adverse events (frequency cannot be estimated from the available data).
† Injection-site adverse reactions

4.9 Overdose

Administration of a higher than recommended dose of ZOSTAVAX was reported rarely and the adverse event 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*).

Evaluation of Clinical Efficacy Afforded by ZOSTAVAX
Shingles Prevention Study (SPS) in Subjects 60 Years of Age and Older:
ZOSTAVAX significantly reduced the risk of developing zoster and PHN compared with placebo. In addition, ZOSTAVAX significantly reduced zoster-associated pain as measured by the HZ pain Burden of Illness (BOI) score (see results and definition in Table 2).

Table 2
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%

*Vaccine efficacy = relative reduction in the endpoint measurement in the vaccine group compared with the placebo group
**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.

In the Shingles Prevention Study (SPS), a placebo-controlled, double-blind clinical trial of ZOSTAVAX, 38546 subjects 60 years of age or older were randomized to receive a single dose of either ZOSTAVAX (n=19270) or placebo (n=19276).

ZOSTAVAX significantly decreased the incidence of zoster compared with placebo (315 [5.4/1000 person-years] vs. 642 cases [11.1/1000 person-years], respectively; p<0.001). The protective efficacy of ZOSTAVAX against zoster was 51% (95% CI: [44 to 58%]). ZOSTAVAX reduced the incidence of zoster by 64% (95% CI: [56 to 71%]) in individuals 60-69 years of age and by 38% (95% CI: [25 to 48%]) in individuals ≥70 years of age.

In the SPS, the reduction in zoster was seen in almost all dermatomes. Ophthalmic zoster occurred in 35 subjects vaccinated with ZOSTAVAX vs. 69 subjects who received placebo. Impaired vision occurred in 2 subjects vaccinated with ZOSTAVAX vs. 9 who received placebo.

ZOSTAVAX decreased the incidence of PHN compared with placebo [(27 cases [0.5/1000 person-years] vs. 80 cases [1.4/1000 person-years], respectively; p<0.001). In this trial, the definition of PHN was clinically significant zoster-associated pain persisting or appearing at least 90 days after the onset of rash. The protective efficacy of ZOSTAVAX against PHN was 67% (95% CI: [48 to 79%]). Referring only to subjects who developed zoster, there was a decrease in 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.

ZOSTAVAX reduced the HZ pain BOI score by approximately 61% (95% CI: [51 to 69%]), compared with placebo. The effect was more pronounced in the younger age group (60 to 69 years) where the efficacy of ZOSTAVAX on HZ pain BOI was 66% compared to 55% in patients ≥70 years of age; however, this difference was not statistically significant (p=0.266).

Prevention of HZ cases with severe pain in the entire 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. The HZ pain severity-by-duration score was 89 (95%CI: [82 to 97%]) for the vaccine group vs. 92 (95% CI: [87 to 97%]) for the placebo group. The overall use of analgesic medication was similar in both study groups.

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).

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 HZ with severe and long-lasting pain (severity-by-duration score of >600).

The Short-term Persistence Substudy (STPS):
The STPS was initiated to accrue additional information on the persistence of vaccine efficacy and to preserve a subset of subjects from the SPS for the long-term persistence substudy (LTPS). The STPS included 7,320 subjects previously vaccinated with ZOSTAVAX and 6,950 subjects previously vaccinated with placebo in the SPS. The mean age at enrollment in the STPS was 73.3 years. During the course of the STPS, placebo recipients were offered ZOSTAVAX, at which time they were considered to have completed the STPS.

The STPS analyses for vaccine efficacy are based on data collected primarily 4 to 7 years postvaccination in the SPS. The median follow-up in the STPS was ~1.2 years (range is one day to 2.2 years). In the STPS, there were 84 evaluable HZ cases [8.4/1000 person-years] in the ZOSTAVAX group and 95 evaluable cases [14.0/1000 person-years] in the placebo group.-The estimated vaccine efficacy during the STPS follow-up period was 40% (95% CI: [18 to 56%]) for HZ incidence, 60% (95% CI: [-10 to 87%]) for PHN incidence and 50% (95% CI: [14 to 71%]) for HZ BOI.

The Long-term Persistence Substudy (LTPS):
Following completion of the STPS, the LTPS evaluated the duration of protection against HZ, PHN and HZ BOI in a total of 6,867 subjects previously vaccinated with ZOSTAVAX in the SPS. The mean age at enrollment into the LTPS was 74.5 years. A concurrent placebo control was not available in the LTPS; data from prior placebo recipients were used to estimate vaccine efficacy.

The LTPS analyses for vaccine efficacy are based on data collected primarily from Year 7 through Year 10 following vaccination in the SPS. The median follow-up during the LTPS was ~3.9 years (range is one week to 4.75 years). There were 263 evaluable HZ cases reported among 261 patients [10.3/1000 person-years] during the LTPS. The estimated vaccine efficacy during the LTPS follow-up period was 21% (95% CI: [11 to 30%]) for HZ incidence, 35% (95% CI: [9 to 56%]) for PHN incidence and 37% (95% CI: [27 to 46%]) for HZ BOI.

ZOSTAVAX Efficacy and Safety Trial (ZEST) in Subjects 50 to 59 Years of Age:
The ZOSTAVAX Efficacy and Safety Trial (ZEST) was 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 70% (95% CI: [54 to 81%]).

<u>Immunogenicity of ZOSTAVAX</u>

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/10^6 PBMCs], p<0.001) were demonstrated. When evaluated at 4 weeks postvaccination, the immunogenicity of the current refrigerator-stable formulation was shown to be similar to the immunogenicity of the earlier frozen formulation 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).

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 split influenza vaccine. The antibody responses to both vaccines at 4 weeks postvaccination were similar, whether administered concomitantly or nonconcomitantly.

In a double-blind, controlled clinical trial, 473 adults, 60 years of age or older, were randomized to receive a single dose of ZOSTAVAX either concomitantly (N=237), or nonconcomitantly with 23-valent pneumococcal polysaccharide vaccine (N=236). At four weeks postvaccination, the VZV antibody levels following concomitant use were not similar to 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])). VZV antibody levels 4 weeks postvaccination were increased 1.9-fold (95% CI: [1.7, 2.1]; meeting the pre-specified acceptance criterion) in the concomitant group vs. 3.1-fold (95% CI: [2.8, 3.5]) in the nonconcomitant group. The GMTs for 23-valent pneumococcal polysaccharide vaccine antigens were similar between the two groups. There was no significant difference in the safety profile between concomitant and nonconcomitant administration of ZOSTAVAX and 23-valent pneumococcal polysaccharide vaccine, except for headache and pneumococcal vaccine injection site erythema and swelling, which were more common in the concomitant group.

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 and safety (see section 4.8) of ZOSTAVAX. ZOSTAVAX induced a significantly higher VZV-specific immune response measured by gpELISA at 4 weeks postvaccination, compared with placebo (2.1-fold difference (95% CI: [1.5 to 2.9]), p<0.001), GMT of 812 vs. 393 gpELISA units/ml. VZV antibody responses were generally similar in subjects 50 to 59 compared to subjects ≥60 years of age.

Immunogenicity in subjects on chronic/maintenance systemic corticosteroids

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX was administered to 206 subjects 60 years of age or older who were receiving chronic/maintenance systemic corticosteroid therapy at a daily dose equivalent of 5 to 20 mg of prednisone for at least 2 weeks prior to enrollment, and 6 weeks or more following vaccination to assess the immunogenicity and safety profile of ZOSTAVAX. Compared with placebo, ZOSTAVAX induced a higher VZV-specific gpELISA antibody GMT at 6 weeks postvaccination (GMT of 531.1 vs. 224.3 gpELISA units/ml, respectively). The Geometric mean

fold-rise of immune response following vaccination as measured by gpELISA was 2.3-fold (95% CI: [2.0 to 2.7]) compared to 1.1-fold (95% CI: [1.0 to 1.2]) in the placebo group.

Revaccination
The need for, or timing of, revaccination with ZOSTAVAX has not yet been determined.

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.

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

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 SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sucrose
Hydrolysed gelatin
Sodium chloride
Potassium dihydrogen phosphate
Potassium chloride
Monosodium L-glutamate
Anhydrous 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 in the same syringe.

6.3 Shelf life

18 months.

After reconstitution, the vaccine should be used immediately. However, the 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 the reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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.

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
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 lyophilized vaccine and gently agitate to mix thoroughly.
Withdraw the entire contents into a syringe for injection.
One or 2 separate needles may be available in the secondary packaging of the presentation containing the pre-filled syringe without the 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.

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 use the reconstituted vaccine if you notice any particulate matter or if the appearance of the solvent or of the reconstituted vaccine differs from that described above.

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

7. MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD, SNC
8, rue Jonas Salk
F-69007 Lyon
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/341/ 003
EU/1/06/341/ 004
EU/1/06/341/ 005
EU/1/06/341/ 006
EU/1/06/341/ 007
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: 23 May 2006
Date of latest renewal: 23 May 2011

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Merck Sharp & Dohme Corp.
Sumneytown Pike
West Point
Pennsylvania 19486
U.S.A.

Name and address of the manufacturer responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information is received that may lead to a significant change to benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached..

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

ZOSTAVAX - Powder in vial and solvent in vial - Pack of 1, 10

1. NAME OF THE MEDICINAL PRODUCT

ZOSTAVAX powder and solvent for suspension for injection
shingles (herpes zoster) vaccine (live)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.65 ml) contains:
Varicella-zoster virus, Oka/Merck strain, (live, attenuated) ≥19400 PFU*
*PFU = Plaque-forming units

3. LIST OF EXCIPIENTS

Sucrose, hydrolysed gelatin, urea, sodium chloride, potassium dihydrogen phosphate, potassium chloride, monosodium L-glutamate, anhydrous disodium phosphate, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection
Pack of 1 single dose vial (powder) + 1 single dose vial (solvent)
Pack of 10 single dose vials (powder) + 10 single dose vials (solvent)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated. Do not freeze. Keep the vial in the outer carton to protect from light.

After reconstitution, use immediately or within 30 minutes if stored at 20°C-25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Read the package leaflet for disposal of medicines no longer required.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8, rue Jonas Salk
F-69007 Lyon
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/341/001 – pack of 1
EU/1/06/341/002 – pack of 10

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ZOSTAVAX powder for suspension for injection
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

SANOFI PASTEUR MSD SNC

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for ZOSTAVAX
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

SANOFI PASTEUR MSD SNC

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

ZOSTAVAX - Powder in vial and solvent in pre-filled syringe with attached needle Pack of 1, 10

1. NAME OF THE MEDICINAL PRODUCT

ZOSTAVAX powder and solvent for suspension for injection in a pre-filled syringe
shingles (herpes zoster) vaccine (live)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.65 ml) contains:
Varicella-zoster virus, Oka/Merck strain, (live, attenuated) ≥19400 PFU*
*PFU = Plaque-forming units

3. LIST OF EXCIPIENTS

Sucrose, hydrolysed gelatin, urea, sodium chloride, potassium dihydrogen phosphate, potassium chloride, monosodium L-glutamate, anhydrous disodium phosphate, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection in a pre-filled syringe
Pack of 1 single dose vial (powder) + 1 pre-filled syringe with attached needle (solvent)
Pack of 10 single dose vials (powder) + 10 pre-filled syringes with attached needle (solvent)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated. Do not freeze. Keep the vial in the outer carton to protect from light.

After reconstitution, use immediately or within 30 minutes if stored at 20°C-25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Read the package leaflet for disposal of medicines no longer required.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8, rue Jonas Salk
F-69007 Lyon
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/341/003 – pack of 1
EU/1/06/341/004 – pack of 10

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

ZOSTAVAX - Powder in vial and solvent in pre-filled syringe without needle - Pack of 1, 10, 20

1. NAME OF THE MEDICINAL PRODUCT

ZOSTAVAX powder and solvent for suspension for injection in a pre-filled syringe
shingles (herpes zoster) vaccine (live)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1dose (0.65 ml) contains:
Varicella-zoster virus, Oka/Merck strain, (live, attenuated) ≥19400 PFU*
*PFU = Plaque-forming units

3. LIST OF EXCIPIENTS

Sucrose, hydrolysed gelatin, urea, sodium chloride, potassium dihydrogen phosphate, potassium chloride, monosodium L-glutamate, anhydrous disodium phosphate, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection in a pre-filled syringe
Pack of 1 single dose vial (powder) + 1 pre-filled syringe without needle (solvent)
Pack of 10 single dose vials (powder) + 10 pre-filled syringes without needle (solvent)
Pack of 20 single dose vials (powder) + 20 pre-filled syringes without needle (solvent)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated. Do not freeze. Keep the vial in the outer carton to protect from light.

After reconstitution, use immediately or within 30 minutes if stored at 20°C-25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Read the package leaflet for disposal of medicines no longer required.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8, rue Jonas Salk
F-69007 Lyon
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/341/005 – pack of 1
EU/1/06/341/006 – pack of 10
EU/1/06/341/007 – pack of 20

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

ZOSTAVAX - Powder in vial and solvent in pre-filled syringe with one unattached needle - Pack of 1, 10, 20

1. NAME OF THE MEDICINAL PRODUCT

ZOSTAVAX powder and solvent for suspension for injection in a pre-filled syringe
shingles (herpes zoster) vaccine (live)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1dose (0.65 ml) contains:
Varicella-zoster virus Oka/Merck strain, (live, attenuated) ≥19400 PFU*
*PFU = Plaque-forming units

3. LIST OF EXCIPIENTS

Sucrose, hydrolysed gelatin, urea, sodium chloride, potassium dihydrogen phosphate, potassium chloride, monosodium L-glutamate, anhydrous disodium phosphate, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection in a pre-filled syringe
Pack of 1 single dose vial (powder) + 1 pre-filled syringe (solvent) + 1 needle unattached needle
Pack of 10 single dose vials (powder) + 10 pre-filled syringes (solvent) + 10 unattached needles
Pack of 20 single dose vials (powder) + 20 pre-filled syringes (solvent) + 20 unattached needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated. Do not freeze. Keep the vial in the outer carton to protect from light.

After reconstitution, use immediately or within 30 minutes if stored at 20°C-25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Read the package leaflet for disposal of medicines no longer required.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8, rue Jonas Salk
F-69007 Lyon
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/341/008 - pack of 1
EU/1/06/341/009 - pack of 10
EU/1/06/341/010 - pack of 20

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

ZOSTAVAX - Powder in vial and solvent in pre-filled syringe with 2 unattached needles - Pack of 1, 10, 20

1. NAME OF THE MEDICINAL PRODUCT

ZOSTAVAX powder and solvent for suspension for injection in a pre-filled syringe
shingles (herpes zoster) vaccine (live)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.65 ml) contains:
Varicella-zoster virus Oka/Merck strain, (live, attenuated) ≥19400 PFU*
*PFU = Plaque-forming units

3. LIST OF EXCIPIENTS

Sucrose, hydrolysed gelatin, urea, sodium chloride, potassium dihydrogen phosphate, potassium chloride, monosodium L-glutamate, anhydrous disodium phosphate, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection in a pre-filled syringe
Pack of 1 single dose vial (powder) + 1 pre-filled syringe (solvent) + 2 unattached needles
Pack of 10 single dose vials (powder) + 10 pre-filled syringes (solvent) + 20 unattached needles
Pack of 20 single dose vials (powder) + 20 pre-filled syringes (solvent) + 40 unattached needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated. Do not freeze. Keep the vial in the outer carton to protect from light.

After reconstitution, use immediately or within 30 minutes if stored at 20°C-25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Read the package leaflet for disposal of medicines no longer required.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8, rue Jonas Salk
F-69007 Lyon
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/341/011– pack of 1
EU/1/06/341/012 – pack of 10
EU/1/06/341/013– pack of 20

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ZOSTAVAX powder for suspension for injection
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

SANOFI PASTEUR MSD SNC

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE OF SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for ZOSTAVAX
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

SANOFI PASTEUR MSD SNC

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

ZOSTAVAX
Powder and solvent for suspension for injection
shingles (herpes zoster) vaccine (live)

Read all of this leaflet carefully before you are vaccinated because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This vaccine has been prescribed for you only. Do not pass it on to others.
- If you get any of the side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What ZOSTAVAX is and what it is used for

ZOSTAVAX is a vaccine used to prevent shingles (zoster) and zoster-related post-herpetic neuralgia (PHN), the long-lasting nerve pain that follows shingles.

ZOSTAVAX is used to vaccinate individuals 50 years of age or older.

ZOSTAVAX cannot be used to treat existing shingles or the pain associated with existing shingles.

Disease information on shingles:

What is shingles?

Shingles is a painful, blistering rash. It usually occurs in one part of the body and can last for several weeks. It may lead to severe and long-lasting pain and scarring. Less commonly, bacterial skin infections, weakness, muscle paralysis, loss of hearing or vision can occur. Shingles is caused by the same virus that causes chickenpox. After you have had chickenpox, the virus that caused it stays in your body in nerve cells. Sometimes, after many years, the virus becomes active again and causes shingles.

What is PHN?

After the shingles blisters heal, pain can last for months or years and may be severe. This long-lasting nerve pain is called post-herpetic neuralgia or PHN.

2. What you need to know before you receive ZOSTAVAX

Do not receive ZOSTAVAX

- if you are allergic (hypersensitive) to any of the components of this vaccine (including neomycin or any of the other ingredients listed in section 6)
- if you have a blood disorder or any type of cancer that weakens your immune system
- if you have been told by your doctor that you have a weakened immune system as a result of a disease, medicines, or other treatment
- if you have active untreated tuberculosis
- if you are pregnant (in addition, pregnancy should be avoided for 1 month after vaccination, see **Pregnancy and breast-feeding**).

Warnings and precautions

If you have experienced any of the following, talk to your doctor or pharmacist before receiving ZOSTAVAX:
- if you have or have had any medical problems or any allergies
- if you have a fever
- if you have HIV infection

As with many vaccines, ZOSTAVAX may not completely protect all persons who are vaccinated.

Other medicines and ZOSTAVAX

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines or vaccines.

ZOSTAVAX can be administered at the same time as inactivated influenza vaccine. The two vaccines should be given as separate injections at different body sites.

ZOSTAVAX should not be given at the same time as the 23-valent pneumococcal polysaccharide vaccine. For more information about these vaccines, talk to your doctor or health care provider.

Pregnancy and breast-feeding

ZOSTAVAX should not be given to pregnant women. Women of child-bearing potential should take the necessary precautions to avoid pregnancy for 1 month following vaccination.

Inform your doctor if you are breast-feeding or intending to breast-feed. Your doctor will decide if ZOSTAVAX should be given.

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before receiving this vaccine.

Driving and using machines

There is no information to suggest that ZOSTAVAX affects the ability to drive or use machines.

Tell your doctor if you have ever had an allergic reaction to any of the ingredients (including neomycin or any of the ingredients listed under “the other ingredients are”- see section 6. Contents of the pack and other information - what ZOSTAVAX contains) before you receive this vaccine.

ZOSTAVAX contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium- free'.

3. How to use ZOSTAVAX

ZOSTAVAX should be injected under the skin, preferably in the upper arm.

ZOSTAVAX is given as a single dose.

Reconstitution instructions intended for healthcare professionals are included at the end of the leaflet.

4. Possible side effects

Like all vaccines and medicines, this vaccine can cause side effects, although not everybody gets them.

In studies, the most commonly reported side effects (occurring in at least 1 in 10 individuals) were at the injection site. These side effects included redness, pain, swelling and itching at the injection site. Headache, pain in arm or leg and warmth, bruising, hard lump at the injection site were also commonly reported (occurring in at least 1 of 100 and less than 1 of 10 individuals). Varicella (chicken pox) was very rarely reported (occurring in less than 1 of 10,000 individuals).

The following additional side effects have been reported in general use with ZOSTAVAX: nausea; joint pain; muscle pain; fever; swollen gland (neck, armpit); rash; rash at the injection site; hives at the injection site; allergic reactions, which may be serious and may include difficulty in breathing or swallowing. If you have an allergic reaction, call your doctor right away.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store ZOSTAVAX

Keep this vaccine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the outer carton after EXP. The expiry date refers to the last day of that month.

Store and transport refrigerated (2°C - 8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ZOSTAVAX contains

After reconstitution, 1 dose (0.65 ml) contains:
The active substance is:
Varicella-zoster virus[1], Oka/Merck strain, (live, attenuated) not less than 19400 PFU (plaque-forming units).
[1] Produced in human diploid (MRC-5) cells

The other ingredients are:

Powder
Sucrose, hydrolysed gelatin, sodium chloride, potassium dihydrogen phosphate, potassium chloride, monosodium L-glutamate, anhydrous disodium phosphate, sodium hydroxide (to adjust pH), and urea.

Solvent
Water for injections

What ZOSTAVAX looks like and contents of the pack

The vaccine is a powder for suspension for injection contained in a single-dose vial, which should be reconstituted with the solvent provided with the vial of powder.

The solvent is a clear and colourless liquid. Before mixing with the solvent, the powder is a white to off-white compact crystalline plug.

ZOSTAVAX is available in packs of 1 or 10. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Sanofi Pasteur MSD SNC, 8 rue Jonas Salk, F-69007 Lyon, France

Manufacturer: Merck Sharp and Dohme, B.V., Waarderweg, 39, 2031 BN Haarlem, The Netherlands

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Sanofi Pasteur MSD, Puh/Tel: +358.9.565.88.30
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United Kingdom
Sanofi Pasteur MSD Ltd, Tel: +44.1.628.785.291

This leaflet was last revised in:

Other sources of information

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

The following information is intended for healthcare professionals only:

Reconstitution instructions

The solvent is a clear and colourless liquid. Before mixing with the solvent, the powder is a white to off-white compact crystalline plug. When completely reconstituted, the vaccine is a semi-hazy to translucent, off-white to pale yellow liquid.

Withdraw the entire volume of solvent into a syringe. Inject the entire content of the syringe into the vial containing the powder. Gently agitate to dissolve completely. Withdraw the entire content of the reconstituted vaccine vial into a syringe for injection.

It is recommended that the vaccine be administered immediately after reconstitution to minimize loss of potency. Discard if reconstituted vaccine is not used within 30 minutes.

Do not use the reconstituted vaccine if you notice any particulate matter or if the appearance of the solvent or powder or of the reconstituted vaccine differs from that described above.

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

See also section 3. How to use ZOSTAVAX.

Package Leaflet: Information for the user

ZOSTAVAX
Powder and solvent for suspension for injection in a pre-filled syringe
shingles (herpes zoster) vaccine (live)

Read all of this leaflet carefully before you are vaccinated because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This vaccine has been prescribed for you only. Do not pass it on to others.
- If you get any of the side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What ZOSTAVAX is and what it is used for

ZOSTAVAX is a vaccine used to prevent shingles (zoster) and zoster-related post-herpetic neuralgia (PHN), the long-lasting nerve pain that follows shingles.

ZOSTAVAX is used to vaccinate individuals 50 years of age or older.

ZOSTAVAX cannot be used to treat existing shingles or the pain associated with existing shingles.

Disease information on shingles:

What is shingles?

Shingles is a painful, blistering rash. It usually occurs in one part of the body and can last for several weeks. It may lead to severe and long-lasting pain and scarring. Less commonly, bacterial skin infections, weakness, muscle paralysis, loss of hearing or vision can occur. Shingles is caused by the same virus that causes chickenpox. After you have had chickenpox, the virus that caused it stays in your body in nerve cells. Sometimes, after many years, the virus becomes active again and causes shingles.

What is PHN?

After the shingles blisters heal, pain can last for months or years and may be severe. This long-lasting nerve pain is called post-herpetic neuralgia or PHN.

2. What you need to know before you receive ZOSTAVAX

Do not receive ZOSTAVAX

- if you are allergic (hypersensitive) to any of the components of this vaccine (including neomycin or any of the other ingredients listed in section 6)
- if you have a blood disorder or any type of cancer that weakens your immune system
- if you have been told by your doctor that you have a weakened immune system as a result of a disease, medicines, or other treatment
- if you have active untreated tuberculosis
- if you are pregnant (in addition, pregnancy should be avoided for 1 month after vaccination, see **Pregnancy and breast-feeding**).

Warnings and precautions

If you have experienced any of the following, talk to your doctor or pharmacist before receiving ZOSTAVAX:
- if you have or have had any medical problems or any allergies
- if you have a fever
- if you have HIV infection

As with many vaccines, ZOSTAVAX may not completely protect all persons who are vaccinated.

Other medicines and ZOSTAVAX

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines or vaccines.

ZOSTAVAX can be administered at the same time as inactivated influenza vaccine. The two vaccines should be given as separate injections at different body sites.

ZOSTAVAX should not be given at the same time as the 23-valent pneumococcal polysaccharide vaccine. For more information about these vaccines, talk to your doctor or health care provider.

Pregnancy and breast-feeding

ZOSTAVAX should not be given to pregnant women. Women of child-bearing age should take the necessary precautions to avoid pregnancy for 1 month following vaccination.

Inform your doctor if you are breast-feeding or intending to breast-feed. Your doctor will decide if ZOSTAVAX should be given.

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before receiving this vaccine.

Driving and using machines

There is no information to suggest that ZOSTAVAX affects the ability to drive or use machines.

Tell your doctor if you have ever had an allergic reaction to any of the ingredients (including neomycin or any of the ingredients listed under “the other ingredients are”- see section 6. Contents of the pack and other information - what ZOSTAVAX contains) before you receive this vaccine.

ZOSTAVAX contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium- free'.

3. How to use ZOSTAVAX

ZOSTAVAX should be injected under the skin, preferably in the upper arm.

ZOSTAVAX is given as a single dose.

Reconstitution instructions intended for healthcare professionals are included at the end of the leaflet.

4. Possible side effects

Like all vaccines and medicines, this vaccine can cause side effects, although not everybody gets them.

In studies, the most commonly reported side effects (occurring in at least 1 in 10 individuals) were at the injection site. These side effects included redness, pain, swelling and itching at the injection site. Headache, pain in arm or leg and warmth, bruising hard lump at the injection site were also commonly reported (occurring in at least 1 of 100 and less than 1 of 10 individuals). Varicella (chicken pox) was very rarely reported (occurring in less than 1 of 10,000 individuals).

The following additional side effects have been reported in general use with ZOSTAVAX: nausea; joint pain; muscle pain; fever; swollen gland (neck, armpit); rash; rash at the injection site; hives at the injection site; allergic reactions, which may be serious and may include difficulty in breathing or swallowing. If you have an allergic reaction, call your doctor right away.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store ZOSTAVAX

Keep this vaccine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the outer carton after EXP. The expiry date refers to the last day of that month.

Store and transport refrigerated (2°C - 8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ZOSTAVAX contains

After reconstitution, 1 dose (0.65 ml) contains:
The active substance is:
Varicella-zoster virus[1], Oka/Merck strain, (live, attenuated) not less than 19400 PFU (plaque-forming units).
[1]Produced in human diploid (MRC-5) cells

The other ingredients are:

Powder
Sucrose, hydrolysed gelatin, sodium chloride, potassium dihydrogen phosphate, potassium chloride, monosodium L-glutamate, anhydrous disodium phosphate, sodium hydroxide (to adjust pH), and urea.

Solvent
Water for injections

What ZOSTAVAX looks like and contents of the pack

The vaccine is a powder for suspension for injection contained in a single-dose vial, which should be reconstituted with the solvent provided with the vial of powder.

The solvent is a clear and colourless liquid. Before mixing with the solvent, the powder is a white to off-white compact crystalline plug.
One pack of ZOSTAVAX contains a vial and a prefilled syringe with or without attached needles. One or 2 separate needles may be available in the secondary packaging of the presentation containing the pre-filled syringe without the attached needle
ZOSTAVAX is available in packs of 1, 10 or 20 with or without needles. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Sanofi Pasteur MSD SNC, 8 rue Jonas Salk, F-69007 Lyon, France

Manufacturer: Merck Sharp and Dohme, B.V., Waarderweg, 39, 2031 BN Haarlem, The Netherlands

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in:

Other sources of information

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

The following information is intended for healthcare professionals only:

Reconstitution instructions

The solvent is a clear and colourless liquid. Before mixing with the solvent, the powder is a white to off-white compact crystalline plug. When completely reconstituted, the vaccine is a semi-hazy to translucent, off-white to pale yellow liquid.

Inject the entire content of the pre-filled syringe into the vial containing the powder. Gently agitate to dissolve completely. Withdraw the entire content of the reconstituted vaccine vial into a syringe for injection. One or 2 separate needles may be available in the secondary packaging of the presentation containing the pre-filled syringe without the 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.

It is recommended that the vaccine be administered immediately after reconstitution to minimize loss of potency. Discard if reconstituted vaccine is not used within 30 minutes.

Do not use the reconstituted vaccine if you notice any particulate matter or if the appearance of the solvent or powder or of the reconstituted vaccine differs from that described above.
Any unused product or waste material should be disposed of in accordance with local requirements.

See also section 3. How to use ZOSTAVAX.