

The legally binding text is the original French version

TRANSPARENCY COMMITTEE
Opinion
15 October 2014

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

B/1 glass vial – 1 glass pre-filled syringe with 2 needles (CIP: 34009 375 930 0 7)

Applicant: SANOFI PASTEUR MSD

| | |
|------------------------|--|
| INN | zoster vaccine (live attenuated) |
| ATC code (2013) | J07BK02 (zoster vaccine) |
| Reason for the request | Inclusion |
| Lists concerned | National Health Insurance (French Social Security Code L.162-17) Hospital use (French Public Health Code L.5123-2) |
| Indications concerned | “ZOSTAVAX is indicated for prevention of herpes zoster (“zoster” or shingles) and herpes zoster-related post-herpetic neuralgia (PHN). ZOSTAVAX is indicated for immunisation of individuals 50 years of age or older.” |

| | |
|-------------------------------|--|
| Actual benefit | <p>In view of:</p> <ul style="list-style-type: none"> - the modest efficacy on the incidence of herpes zoster in the populations recommended by the Haut Conseil de la Santé Publique [French Public Health Council] (HCSP), - the decrease in vaccine protection with age and over time, - the contraindication of vaccination in immunocompromised subjects, <p>the Committee considers that the actual benefit of ZOSTAVAX is <u>moderate</u> in the prevention of zoster and post-herpetic neuralgia, in the populations recommended by the HCSP.</p> |
| Improvement in actual benefit | <p>ZOSTAVAX provides a <u>minor</u> clinical added value, level IV) in the prevention of herpes zoster, in the populations recommended by the HCSP.</p> |
| Therapeutic use | <p>ZOSTAVAX is reserved for the vaccination of adults aged 65 to 74 years with a one-dose vaccination regimen. During the first year following inclusion of the vaccine in the vaccination calendar, individuals aged 75 to 79 years might also be vaccinated.</p> |

01 ADMINISTRATIVE AND REGULATORY INFORMATION

| | |
|---------------------------------------|---|
| Marketing Authorisation | <p>Initial date (centralised procedure): 19 May 2006, for the frozen form, for vaccination of individuals aged 60 years and over</p> <p>Variationss:</p> <ul style="list-style-type: none"> - 3 January 2007: refrigerated vaccine concomitant administration possible with the influenza vaccine - 24 July 2007: extension of indication to individuals aged 50 years and over - 28 July 2008: possible administration after a previous episode of zoster - 21 February 2012: possible administration to patients treated with low-dose corticosteroids <p>The Marketing Authorisation is associated with a RMP.</p> |
| Prescribing and dispensing conditions | List I |

| | |
|--------------------|---|
| ATC Classification | <p>2013 J Antiinfectives for systemic use J07 Vaccines J07B Viral vaccines J07BK Varicella zoster vaccines J07BK02 zoster, live attenuated</p> |
|--------------------|---|

02 BACKGROUND

Examination of the initial request for inclusion of the proprietary medicinal product ZOSTAVAX, powder and solvent for suspension for injection in a pre-filled syringe, on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

ZOSTAVAX is a live attenuated vaccine against varicella zoster virus (VZV) produced in human diploid cells (MRC5) from the same strain as the live attenuated vaccine used in the prevention of varicella, VARIVAX (OKA strain), with a titre 14 times higher after reconstitution (19,400 plaque-forming units (PFU) for ZOSTAVAX versus 1350 PFU for VARIVAX). This is the first vaccine indicated for the prevention of zoster and post-herpetic neuralgia (PHN) in individuals aged 50 years and over.

In December 2006, the Conseil supérieur d'hygiène publique de France [French Council for Public Health] (CSHPF) considered that mass vaccination with the ZOSTAVAX vaccine could not be recommended for the following reasons:¹

- a correlation has not been demonstrated between the immunity obtained and clinical protection;

¹ CSHPF opinion concerning the zoster vaccine.

http://www.sante.gouv.fr/IMG/pdf/Avis_du_22_septembre_2006_et_du_5_decembre_2006_relatif_au_vaccin_contre_le_zona.pdf.

- the duration of the protection conferred is unknown and it is therefore unknown whether there is any delay in the age at which zoster occurs or whether a booster dose is needed;
- the storage conditions before reconstitution (freezing);
- the availability of antiviral treatments whose early use helps to reduce pain in the initial phase of the disease and the occurrence of post-herpetic neuralgia.

The CSHPF had stated that it would reconsider its position once data were available on the long-term efficacy and value of a possible booster vaccine.

In 2013, after new data on efficacy were obtained and a form that could be stored in a refrigerator became available, the HCSP initiated its own examination to determine the role of this vaccine within the context of current adult vaccination strategies. Following this examination, the HCSP recommended vaccination against zoster in individuals aged 65 to 74 years (see Appendix).^{2,3}

“The Haut Conseil de la Santé Publique recommends vaccination against zoster in adults aged 65 to 74 years with a one-dose vaccination regimen. During the first year after the inclusion of the vaccine in the vaccination calendar, individuals aged 75 to 79 years can be vaccinated as part of a catch-up phase.

This live vaccine, consisting of an attenuated viral strain of the varicella zoster virus, is contraindicated in immunosuppressed individuals.

The need for a booster dose is currently unknown.”

03 THERAPEUTIC INDICATIONS (EXTRACT OF SPC)

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

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

04 DOSAGE (EXTRACT OF SPC)

“Individuals should receive a single dose (0.65 ml) administered subcutaneously.

The need for a second dose is currently unknown.

Paediatric population:

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

05 INTERACTIONS WITH OTHER VACCINES (EXTRACT OF SPC)

“ZOSTAVAX can be administered concomitantly with inactivated influenza vaccine as separate injections and at different body sites.

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.

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

² HCSP Opinion of 25 October 2013 relating to the vaccination of adults against zoster with Zostavax vaccine. <http://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=390>.

³ HCSP Report of 25 October 2013. Vaccination of adults against zoster. Use of Zostavax vaccine. <http://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=390>.

06 THERAPEUTIC NEED^{4,5}

Varicella zoster virus (VZV) is a virus from the *Herpesviridae* family capable of entering the peripheral nervous system during primary infection and establishing a latent infection that may, in some cases, cause reactivation of the virus.

Varicella is the clinical expression of primary infection by VZV. It is characterised by a maculovesicular rash which usually has a favourable course. It is a highly contagious infection which usually occurs during childhood (90% of cases occur before the age of 15 years). VZV is transmitted during varicella by the vesicles and above all by the oropharyngeal route. The transmission period begins 2 to 3 days before vesicle appearance and continues for 4 to 5 days afterwards.

Zoster is caused by the reactivation of the VZV, which has remained latent in the spinal ganglia of the spinal cord after the primary infection. It occurs only in individuals who have previously had varicella and generally appears only once, in adulthood (60% of cases occur after the age of 45 years).

In the acute phase, zoster is manifested as unilateral nerve pain accompanied by a vesicular rash, generally limited to the dermatome corresponding to the sensory ganglion in which the virus has reactivated. The lesions are usually localised on the thorax (more than 60% of cases) but more severe forms can also affect the eyes (approximately 5 to 10%) or ears. The pain in the acute phase is a mixed pain, with an inflammatory component (described as cutting or throbbing) and a neuropathic component (like an electric shock or dynamic mechanical allodynia). The natural course of the acute phase is usually favourable within 2 to 3 weeks. Transmission of VZV is possible by direct contact during the week following the vesicular rash.

The main complication of zoster are persistent neuropathic pain (mainly burning or dynamic mechanical allodynia) in a dermatome corresponding to that affected during the acute phase. This pain is defined as “post-herpetic neuralgia” (PHN) when it lasts more than 1, 3 or 4 months after the skin rash, depending on definitions. There is no consensus on the time after which the pain can be defined as PHN, but persistence for more than 3 months after the rash is the usual definition.⁶ It is associated with a variable sensory deficit and even paraesthesia or dysaesthesia. Other less common but more severe systemic complications can also occur, mainly in immunosuppressed individuals. If the eyes are affected, this can lead to a permanent reduction in visual acuity or even blindness. The most severe forms affecting the ears (Ramsay Hunt syndrome) can cause peripheral facial paralysis. Other neurological complications are very rare: meningitis, motor disorders, Guillain-Barré syndrome, hemiplegia affecting the opposite side to the skin lesions, or diaphragmatic paralysis. Zoster may also take a systemic form, with a combination of extensive skin involvement and visceral involvement (myocarditis, pericarditis, encephalitis, etc.). Local complications related to bacterial superinfection of the lesions are uncommon (2%).

The precise causes of VZV reactivation are not clearly understood but it seems to be favored by a reduction in anti-VZV specific cell immunity. The main risk factors for zoster are therefore age (immunosenescence), diseases that can cause immune deficiency (HIV or cancer) and corticosteroid and immunosuppressive treatments. Other risk factors have also been reported (female gender, stressful events, heredity, etc.). On the other hand, endogenous stimulation (VZV

⁴ Collège des universitaires de maladies infectieuses et tropicales (France), Pilly E, Garré M. ECN. Pilly, Maladies infectieuses et tropicales: in press ECN, all articles on infectious diseases, clinical dossiers, critical review. Paris: Vivactis plus; 2012.

⁵ Ministry of Health - INPES. Guide des vaccinations. Edition 2012. Available on line:

http://www.inpes.sante.fr/10000/themes/vaccination/guide-vaccination-2012/pdf/GuideVaccinations2012_Vaccination_contre_le_zona.pdf.

⁶ Cunningham AL, Dworkin RH. The management of post-herpetic neuralgia. If early treatment fails, patients should be referred to pain clinics. *BMJ* 2000; 321: 778-9.

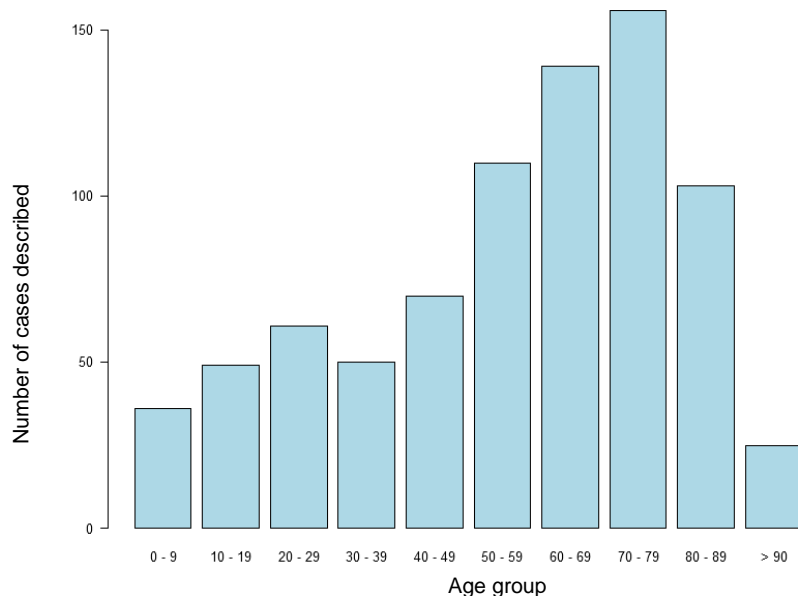
reactivation) or exogenous stimulation (contact with individuals who have varicella) of anti-VZV specific cell immunity seem to provide some protection.

The risk factors for developing PHN are advanced age, prodromes before the appearance of the rash, rash severity, initial intensity of the pain and eye involvement.

In France, the seroprevalence^{7,8} of VZV in the general adult population exceeds 95% and 1.3 to 5 cases of zoster per 1000 inhabitants are observed annually. The lifetime risk of developing zoster in the general population is 10 to 30%, depending on studies.^{9,10}

According to surveillance data from the INSERM Sentinelles network,¹¹ the incidence of first consultations for zoster in the acute phase was 478 per 100,000 inhabitants in 2012, i.e. approximately 304,000 cases of zoster, of which 5.9% were ophthalmic zoster. Almost 70% of patients have received oral antiviral treatment and 5% local treatment. The incidence of zoster increases with age: approximately two-thirds of zoster cases occur after the age of 50 years, with half occurring in patients aged 60 and over with an incidence of 5 to 10 cases per 1000 inhabitants. In 2012, the incidence of zoster after 65 years was estimated at 130,000 cases.

Figure 1: Distribution of zoster cases by age group in France in 2012, according to the Sentinelles network review¹¹



According to studies, PHN is observed in 12 to 28% of cases after 90 days.³

There is currently no preventive treatment available for zoster and post-herpetic neuralgia. Only some antivirals can be used in the treatment of zoster.

⁷ Sengupta N, Booy R, Schmitt HJ, Peltola H, Van-Damme P, Schumacher RF, Campins M, Rodrigo C, Heikkinen T, Seward J, Jumaan A, Finn A, Olcén P, Thiry N, Weil-Olivier C, Breuer J. Varicella vaccination in Europe: are we ready for a universal childhood programme? *Eur J Pediatr* 2008; 167: 47-55.

⁸ Khoshnood B, Debruyne M, Lançon F, Emery C, Fagnani F, Durand I, Floret D. Seroprevalence of varicella in the French population. *Pediatr Infect Dis J* 2006; 25: 41-4.

⁹ Brisson M, Edmunds WJ, Law B, Gay NJ, Walld R, Brownell M, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. *Epidemiol Infect* 2001; 127: 305-14.

¹⁰ Kimberlin DW, Whitley RJ. Varicella-Zoster vaccine for the prevention of herpes zoster. *N Eng J Med* 2007; 356: 1338-43.

¹¹ Réseau Sentinelles. Annual review 2012. Available on line:

<http://websenti.u707.jussieu.fr/sentiweb/?page=bilan>.

07 CLINICALLY RELEVANT COMPARATORS

07.1 Medicinal products

No medicinal products has a Marketing Authorisation for the prevention of herpes zoster.

Some antivirals can be used in the treatment of zoster. These are:

| NAME (INN) | Indications | Use |
|--|---|-----|
| ZOVIRAX and its generics (Aciclovir) | - treatment of VZV infections in immunosuppressed individuals - treatment of severe zoster due to the extent or advanced nature of the lesions, in immunocompetent individuals - prevention of the eye complications of ophthalmic zoster | Yes |
| ORAVIR (Famciclovir) | - treatment of zoster and ophthalmic zoster in immunocompetent adult patients - treatment of zoster in immunosuppressed adult patients | Yes |
| ZELITREX and its generics (Valaciclovir) | - treatment of zoster and ophthalmic zoster in immunocompetent adults - treatment of zoster in adult patients with mild or moderate immunosuppression | Yes |

► Conclusion

There are no medicinal products available with Marketing Authorisation in the prevention of zoster and post-herpetic neuralgia.

08 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

| Country | FUNDING | |
|----------------|------------------|-------------------|
| | Yes/No | Population |
| Germany | No | 50 years and over |
| Australia | Under evaluation | 60 to 79 years |
| Austria | No | 50 years and over |
| Canada | Under evaluation | 60 years and over |
| USA | Yes | 60 years and over |
| Greece | No | 60 years and over |
| United Kingdom | Yes | 70 to 79 years |
| Netherlands | Under evaluation | 70 to 79 years |
| Switzerland | No | 70 to 79 years |
| Sweden | Yes | 50 years and over |

09 ANALYSIS OF AVAILABLE DATA

In support of its request, the company has submitted efficacy and safety data on ZOSTAVAX from the following studies:

- In adults aged 60 and over:
 - Study 004 or SPS (Shingles Prevention Study):¹² a phase III, placebo-controlled, randomised, double-blind study evaluating the efficacy and safety of ZOSTAVAX in individuals aged 60 and over;
 - Follow-up studies evaluating short- and long-term vaccine protection duration:
 - Study 004-05 or STPS (Short-Term Persistence Substudy):¹³ evaluating the duration of vaccine protection in a group of subjects from the SPS followed-up for 4 to 7 years after vaccination;
 - Study 013 or LTPS (Long-Term Persistence Study): evaluating the duration of vaccine protection in a group of subjects from the SPS followed-up for 7 to 10 years after vaccination.
- In adults aged 50 to 59 years:
 - Study 022 or ZEST (ZOSTAVAX Efficacy and Safety Trial):¹⁴ phase III, placebo-controlled, randomised, double-blind trial which evaluated the efficacy, immunogenicity and safety of the vaccine in subjects aged 50 to 59 years.

Studies which evaluated the immunogenicity and safety of ZOSTAVAX in specific situations have also been submitted:

- Study 010,¹⁵ comparing the refrigerated and frozen forms of the vaccine;
- Study 011,¹⁶ comparing concomitant or sequential administration with the influenza vaccine;
- Study 012,¹⁷ comparing concomitant or sequential administration with the 23-valent pneumococcal vaccine;
- Study JV-1,¹⁸ comparing the administration of one and two doses of the vaccine in subjects aged 70 and over;
- Studies 014¹⁹ and 004-08,²⁰ conducted in subjects with a history of zoster;

¹² Oxman MN, Levin MJ, Johnson GR, et al. A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in older Adults. *N Engl J Med* 2005; 352: 2271-84.

¹³ Schmader KE, Oxman MN, Levin MJ, et al. Persistence of the Efficacy of Zoster Vaccine in the Shingles Prevention Study and the Short-Term Persistence Substudy. *Clinical Infectious Diseases Advance Access* published July 24, 2012.

¹⁴ Schmader KE, Myron JL, Gnannjr JW, et al. Efficacy, Safety, and Tolerability of Herpes Zoster Vaccine in Persons Aged 50-59 Years. *Clin Infect Dis*. 2012 Apr; 54(7): 922-8. Epub 2012 Jan 30.

¹⁵ Gilderman LI, Lawless JF, Nolen TM, et al. A Double-Blind, Randomized, Controlled, Multicenter Safety and Immunogenicity Study of a Refrigerator-Stable Formulation of Zostavax. *Clinical and Vaccine Immunology*. 2008 Feb; 15(2): 314-9.

¹⁶ Kerzner B, Murray AV, Cheng E, et al. Safety and Immunogenicity Profile of the Concomitant Administration of Zostavax and Inactivated Influenza Vaccine in Adults Aged 50 and Older. *JAGS* 55: 1499-1507, 2007.

¹⁷ MacIntyre CR, Egerton T, McCaughey M, et al. Concomitant administration of zoster and pneumococcal vaccines in adults \geq 60 years old. *Hum Vaccin*. 2010; 6: 894-902.

¹⁸ Vesikari T et al. Immunogenicity and safety of a live attenuated shingles (herpes zoster) vaccine (Zostavax) in individuals aged \geq 70 years: a randomized study of a single dose versus two different two-doses schedules. *Hum Vaccin Immunother* 2013; 9: 1-7

¹⁹ Mills R, Tyring SK, Levin MJ, et al. Safety, tolerability, and immunogenicity of zoster vaccine in subjects with a history of herpes zoster. *Vaccine* 2010 Jun 7; 28(25): 4204-9. Epub 2010 Apr 21.

- Study²¹ conducted in subjects who were VZV-seronegative or weakly seropositive to VZV;
- Study 017, conducted in subjects receiving long-term corticotherapy;
- Study 002, conducted in subjects with COPD or diabetes.

The results of immunogenicity studies conducted in specific situations have been added to the Clinical Guidelines and will not be given in detail in view of the absence of correlates of protection established in VZV infection.

Observational studies^{22,23,24} conducted retrospectively from US databases have also been submitted.

09.1 Efficacy

9.1.1 In adults aged 60 and over

9.1.1.1 SPS (Shingles Prevention Study)¹²

Objective:

The primary endpoint of the SPS was to determine whether vaccination with ZOSTAVAX would reduce the incidence and/or severity of zoster and PHN in adults aged 60 or over.

Method:

This was a multicentre, placebo-controlled, randomised, double-blind study conducted in the USA, between November 1998 and April 2004.

Study population:

Non-immunosuppressed individuals aged over 60 with a history of varicella but without a history of zoster could be included in this study.

Vaccination:

The subjects were randomised into two groups (vaccine or placebo at D0) in a 1 : 1 ratio with stratification by age (60-69 years and ≥ 70 years) and by site.

Antiviral treatment with famciclovir was offered to the patients with zoster diagnosed less than 72 hours after the skin rash onset; analgesic treatment was left to the investigator's discretion.

Endpoint criteria:

The primary efficacy endpoint was a composite criterion taking into account the incidence, severity and duration of zoster-associated pain along with zoster-related discomfort: the Burden of Illness (BOI) score,²⁵ evaluated for the 6 months after diagnosis of zoster. The incidence of PHN²⁶ was the primary co-criterion. The secondary endpoints were:

²⁰ Morrison VA, Oxman MN, Levin MJ, et al. Safety of Zoster Vaccine in Elderly Adults Following Documented Herpes Zoster. 2013 Aug 15; 208(4): 559-63. doi: 10.1093/infdis/jit182. Epub 2013 Apr 30.

²¹ Macaladad N, Marcano T, Guzman M, et al. Safety and immunogenicity of a zoster vaccine in varicella-zoster virus seronegative and low-seropositive healthy adults. *Vaccine* 2007; 25: 2139-44.

²² Tseng HF et al, Herpes Zoster Vaccine in Older Adults and the Risk of Subsequent Herpes Zoster Disease. *JAMA* 2011; 305: 160-166.

²³ Langan SM, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. *PLoS Med.* 013; 10(4): e1001420.

²⁴ Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, Saag KG, Baddley JW, Curtis JR. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. *JAMA.* 2012 Jul 4; 308(1): 43-9.

²⁵ The BOI score is a composite score calculated from the area under the curve of the severity of the disease as a function of time. The severity of the disease is estimated from the score given by the patient to the maximum pain experienced in the previous 24 hours on a scale from 0 (no pain) to 10 (worst pain)

- the incidence of zoster;
- the duration of zoster-associated pain;²⁷
- the impact of zoster on daily life.²⁸

Statistical analysis:

The number of subjects required was estimated at 37,200 (18,600 per group) for a mean follow-up of 4.5 years taking into account an annual zoster incidence of 3/1000 in subjects in the placebo group and an annual lost to follow-up rate of 10%, considering that:

- 400 cases of zoster should be observed to detect a reduction in the BOI score with 94% power and a 5% alpha risk;
- 62 cases of PHN should be observed to evaluate the incidence of PHN with 96% power and a 5% alpha risk.

An analysis conducted in June 2003 of the first 223 evaluable cases of zoster led to an adjustment of the number of cases of zoster required to 750 as the hypotheses initially adopted to calculate the BOI score were confirmed.

The primary analysis of efficacy criteria concerned the modified intention-to-treat population (MITT), including all randomised subjects and excluding subjects who left the study or who developed zoster in the 30 days following vaccination. The denominator used in the principal analysis was the number of subjects included.

Results:

Overall 38,546 subjects aged over 60 were randomised to receive one dose of ZOSTAVAX (n=19,270) or placebo (n=19,276). The median age of the subjects on inclusion was 69 years: 59% were between 60 and 69, and 41% were 70 or over.

The MITT analysis concerned 38,501 subjects, 19,254 in the vaccine group and 19,247 in the placebo group.

Zoster was diagnosed according to clinical criteria.

The BOI score (primary endpoint) was 2.21 in the ZOSTAVAX group versus 5.68 in the placebo group. Vaccine efficacy based on the BOI score was 61% (95% CI [51.1; 69.1]; p<0.001). It was 66% in subjects aged 60 to 69 and 55% in subjects aged 70 and over (NS).

The incidence of zoster was 315 cases [5.4/1000 person-years] in the ZOSTAVAX group versus 642 in the placebo group [11.1/1000 person-years] corresponding to a protective efficacy against zoster of 51.3% (95% CI [44.2; 57.6]; p<0.001), i.e. an absolute reduction of 5.7 cases of zoster per 1000 person-years. This efficacy was 63.9% (95% CI [55.5; 70.9] in subjects aged 60 to 69, i.e. an absolute reduction of 6.9 cases of zoster per 1000 person-years, and 37.6% (95% CI [25.0; 48.1]) in subjects aged over 70, i.e. an absolute reduction of 4.3 cases of zoster per 1000 persons-year (p<0.001).

The incidence of PHN persisting for more than 3 months after the skin rash was 27 cases [0.5/1000 person-years] in the vaccinated group versus 80 cases [1.4/1000 person-years] in the placebo group corresponding to a vaccine efficacy against PHN of 66.5% (95% CI [47.5; 79.2]; p<0.001) and an absolute reduction of 0.92 cases of PHN per 1000 persons-year.

imaginable). It was estimated about every other day up to D11 of the rash, then once a week up to W8; it was then estimated once a week if the score exceeded 3 or at least at W10, W12 and then every 4 weeks up to W26.

²⁶ In the SPS, PHN is defined as zoster-associated pain that is persistent or appearing more than 3 months after skin rash onset.

²⁷ In the SPS, pain is considered clinically significant if the patient gives a score ≥ 3 to the maximum pain experienced in the 24 hours before assessment on a scale from 0 (no pain) to 10 (worst pain imaginable).

²⁸ In the SPS, the impact of zoster on activities of daily living is estimated by a score (ADLI or "Activities of Daily Living Interference" score) from 0 (no interference) to 10 (maximum interference); the impact is judged to be clinically significant for an ADLI score ≥ 2 for at least 7 days in the 6 months after the skin rash.

Table 1: SPS – Vaccine efficacy based on the primary endpoints and zoster incidence (MITT population)

| | ZOSTAVAX n=19,254 | | Placebo n=19,247 | | Efficacy* [95% CI] |
|---|---------------------------|------|---------------------------|-------|-----------------------|
| Number of zoster cases | 315 | | 642 | | |
| Number of PHN cases | 27 | | 80 | | |
| BOI score** (primary endpoint) | Total | 2.21 | Total | 5.68 | 61.1% [51.1; 69.1] |
| | 60-69 years (n=10,370) | 1.50 | 60-69 years (n=10,356) | 4.33 | 65.5% [51.5; 75.5] |
| | ≥ 70 years (n=8884) | 3.47 | ≥ 70 years (n=8891) | 7.78 | 55.4% [39.9; 66.9] |
| Incidence of PHN (per 1000 patient-years) | Total | 0.46 | Total | 1.38 | 66.5% [47.5; 79.2] |
| | 60-69 years (n=10,370) | 0.26 | 60-69 years (n=10,356) | 0.74 | 65.7% [20; 87] |
| | ≥ 70 years (n=8884) | 0.71 | ≥ 70 years (n=8891) | 2.13 | 66.8% [43; 81] |
| Incidence of zoster (per 1000 patient-years) | Total | 5.42 | Total | 11.12 | 51.3% [44.2; 57.6] |
| | 60-69 years (n=10,370) | 3.90 | 60-69 years (n=10,356) | 10.79 | 63.9% [55.5; 70.9] |
| | ≥ 70 years (n=8884) | 7.18 | ≥ 70 years (n=8891) | 11.50 | 37.6% [25.0; 48.1] |

* The efficacy of the vaccine is defined as the percentage reduction in the criterion evaluated or its incidence compared with the comparator group (placebo).

** The BOI score for each treatment group is the mean of the individual scores, weighted by the number of subjects in each group, stratified by age; a score of 0 was given to subjects who did not have zoster.

Considering only subjects who had zoster (a prerequisite for the appearance of PHN), the incidence of PHN was 8.6% (27/315) in the vaccinated group versus 12.5% in the placebo group (80/642). In a *post hoc* analysis adjusted for age performed by the FDA,²⁹ the relative reduction in the incidence of PHN in vaccinated subjects who had zoster was 39% (95% CI [7; 59]). According to the analysis by age group, the relative reduction was 5% (95% CI [-107; 56]) in subjects aged 60 to 69 (6.6% (8/122) PHN in the vaccinated group versus 6.9% (23/334) in the placebo group), 55% relative reduction of PHN (95% CI [18; 76]) in subjects aged 70 to 79 (7.7% (12/156) PHN in the vaccinated group versus 17.2% (45/261) in the placebo group) and 26% relative reduction of PHN (95% CI [-69; 68]) in subjects aged over 80 (18.9% (7/37) PHN in the vaccinated group versus 25.5% (12/47) in the placebo group).

The median duration of zoster-associated pain of intensity ≥ 3 (on a scale from 0 to 10) was reduced by 2 days in the vaccinated group (20 days versus 22 days; p<0.001). No differences were observed concerning the impact of zoster on daily life.

9.1.1.2 STPS (Short-Term Persistence Substudy)¹³ and LTPS (Long-Term Persistence Study)

Two SPS follow-up studies were conducted under open-label conditions: the STPS, between October 2005 and March 2006, then the LTPS, between March 2006 and February 2011.

²⁹ FDA. ZOSTAVAX SPC and leaflet.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM132831.pdf>.

Overall, 21,198 subjects from the SPS were contacted and invited to take part in the STPS. 14,270 of these subjects were included: 7320 previously vaccinated with ZOSTAVAX and 6950 having previously received a placebo. Vaccination with ZOSTAVAX was offered to subjects who had received a placebo. The 6867 initially vaccinated subjects who completed the SPS follow-up were included in the LTPS.

Table 2: SPS and STPS – Vaccine efficacy based on the primary endpoints and zoster incidence

| Period | Numbers | | BOI score [95% CI] | PHN incidence [95% CI] | Zoster incidence [95% CI] |
|-------------|----------|---------|------------------------|---------------------------|------------------------------|
| | ZOSTAVAX | Placebo | | | |
| Year 1 | 19,254 | 19,247 | 79.2% [66.8; 86.9] | 83.4% [56.7; 95.0] | 62.0% [49.6; 71.6] |
| Year 2 | 19,024 | 18,948 | 54.9% [32.0; 70.1] | 69.8% [27.3; 89.1] | 48.9% [34.7; 60.1] |
| Year 3 | 18,692 | 18,494 | 44.4% [17.6; 62.5] | 38.3% [-44.7; 75.0] | 46.8% [31.1; 59.2] |
| Year 4 | 11,689 | 11,474 | 66.9% [37.5; 82.5] | 60.7% [-36.3; 91.0] | 44.6% [20.5; 61.8] |
| Year 5 | 7197 | 6887 | 74.9% [48.6; 87.7] | 73.8% [-37.8; 97.3] | 43.1% [5.1; 66.5] |
| Year 6 | 7086 | 6055 | 23.6% [-58.1; 63.1] | 32.0% [-100.0; 87.3] | 30.6% [-6.0; 54.6] |
| Year 7* | 4054 | 2237 | 72.5% [9.9; 91.6] | 60.0% [-4.5; 97.1] | 52.8% [-16.5; 80.5] |
| Years 1 - 7 | 19,254 | 19,247 | 50.1% [14.1; 71.0] | 60.1% [-9.8; 86.7] | 39.6% [18.2; 55.5] |

* Year 7 included a small number of events and person-years monitored during year 8

The non-randomised LTPS yielded follow-up data up to 12 years after vaccination. Overall, 6043 subjects completed the follow-up. The mean duration of the follow-up was 9.76 years and the median duration 10 years.

Vaccine efficacy estimated in relation to theoretical values during the LTPS follow-up period was 21.1% (95% CI [10.9; 30.4]) for zoster incidence, 35.4% (95% CI [8.8; 55.8]) for PHN incidence and 37.3% (95% CI [26.7; 46.4]) for the BOI score.

9.1.2 In adults aged 50 to 59 years

9.1.2.1 ZEST (ZOSTAVAX Efficacy and Safety Trial)¹⁴

Endpoint:

The primary endpoint of the ZEST was to evaluate the impact of vaccination with ZOSTAVAX on zoster incidence in adults aged 50 to 59 years.

Method:

This was a multicentre, placebo-controlled, randomised study conducted under double-blind conditions between October 2007 and January 2010.

Study population:

Non-immunosuppressed subjects aged 50 to 59 years with a history of varicella but without a history of zoster could be included in this study.

Vaccination:

The subjects were randomised into two groups (vaccine or placebo at D1) in a 1 : 1 ratio.

Endpoint criteria:

The primary efficacy endpoint was zoster incidence.

Statistical analysis:

The primary analysis of efficacy criteria concerned the intention-to-treat (ITT) population.

Results:

Overall, 22,439 subjects aged 50 to 59 years were randomised to receive one dose of ZOSTAVAX (n=11,211) or placebo (n=11,228). The median age of the subjects on inclusion was 55 years.

The diagnosis of herpes zoster was established by a clinical evaluation committee then validated by polymerase chain reaction (PCR) in the majority of cases (86%).

Table 3: ZEST – Zoster incidence (ITT population)

| | ZOSTAVAX n=11,211 | Placebo n=11,228 | Efficacy [95% CI] |
|--|----------------------|---------------------|-----------------------|
| Number of zoster cases | 30 | 99 | |
| Zoster incidence (per 1000 patient-years) | 1.99 | 6.60 | 69.8% [54.1; 80.6] |

The incidence of zoster was 30 cases [2.0/1000 person-years] in the ZOSTAVAX group versus 99 in the placebo group [6.6/1000 person-years] corresponding to an efficacy in terms of protection against zoster of 69.8% (95% CI [54.1; 80.6]), i.e. an absolute reduction of 4.6 cases of zoster per 1000 person-years.

9.1.3 Observational studies

The results of 3 observational studies conducted retrospectively from US databases were also submitted by the company:

- the study by Tseng *et al.*²²

This study evaluated the risk of zoster occurring after vaccination in immunocompetent subjects aged 60 and over based on a retrospective analysis of data from KPSC (Kaiser Permanente Southern California) relating to 75,761 vaccinated subjects paired with 227,283 unvaccinated subjects, between 1 January 2007 and 31 December 2009. The mean age of the subjects included was 69.6 years. Zoster incidence was 6.4/1000 person-years (95% CI [5.9; 6.8]) in the vaccinated subjects versus 13.0/1000 person-years (95% CI [12.6; 13.3]) in the unvaccinated subjects. According to an analysis adjusted for age, gender, race, treatment type and comorbid chronic illnesses, vaccination was associated with a reduction in the risk of zoster (HR = 0.45; 95% CI [0.42; 0.48]) and ophthalmic zoster (HR = 0.37; 95% CI [0.23; 0.61]).

- the study by Langan *et al.*²³

This study evaluated vaccine efficacy against zoster incidence after vaccination in immunocompetent or immunosuppressed subjects aged 65 and over based on a retrospective analysis of data from 766,330 Medicare beneficiaries including 29,785 who had been vaccinated, between 1 January 2007 and 31 December 2009. Zoster incidence was 5.4/1000 person-years (95% CI [4.6; 6.4]) in vaccinated subjects versus 10.0/1000 person-years (95% CI [9.8; 10.2]) in unvaccinated subjects. According to an analysis adjusted for age, gender, race, income level, immunosuppression and chronic illnesses, vaccine efficacy against zoster was 48% (95% CI [39; 56]).

- the study by Zhang *et al.*²⁴

This study evaluated the risk of zoster occurring after vaccination in subjects with autoimmune diseases aged 60 and over, based on a retrospective analysis of data from 463,541 Medicare beneficiaries (292,169 with rheumatoid arthritis, 11,030 with psoriatic arthritis, 89,565 with psoriasis, 66,751 with chronic inflammatory bowel disease and 4026 with ankylosing spondylitis) including 18,683 who had been vaccinated, between 1 January 2006 and 31 December 2009. The mean age of the subjects included was 74 years. Zoster incidence was 7.8/1000 person-years (95% CI [3.7; 16.5]) in vaccinated subjects versus 11.6/1000 person-years (95% CI [11.4; 11.9]) in unvaccinated subjects. According to an analysis adjusted for demographic characteristics, autoimmune disease type, treatment type and co-treatments, vaccination was associated with a reduction in the risk of zoster (HR = 0.61; 95% CI [0.52; 0.71]).

In view of the methodology of these studies and the differences in vaccination strategy between France and the USA (vaccination against varicella implemented since 1995 in the USA), these results should be interpreted with caution.

09.2 Adverse effects

9.2.1 Clinical study data

The safety of ZOSTAVAX has been evaluated in clinical studies in approximately 57,000 adults aged 50 and over.

SPS:

The adverse events most frequently reported among the 19,270 subjects aged 60 and over who received one dose of ZOSTAVAX were transient local reactions such as erythema (35.8%), pain (34.5%) or swelling (26.2%). These reactions were significantly more frequent in the vaccinated group. Systemic reactions considered possibly related to the vaccine were reported in 6.3% of cases. These reactions were mainly headaches.

During the 42 days following the injection, the number and type of serious adverse events reported were comparable in the two treatment groups. Varicella-like rashes at the injection site was reported more frequently in the vaccinated group than in the placebo group (20 cases, i.e. 0.1% versus 7 cases, i.e. 0.04%), but generalised rashes were reported with a similar frequency in both groups (18 cases, i.e. 0.1% versus 14 cases, i.e. 0.1%). VZV was not detected in any of the 10 samples available and analysed by PCR. Zoster-like rashes were less frequent in the vaccinated group (17 versus 36). Wild-type VZV was detected in 25 of the 41 samples available and analysed by PCR (5 for ZOSTAVAX, 20 for placebo). The vaccine strain of VZV was not detected in any of these samples.

Two serious adverse effects considered vaccine-related were reported: one case of polymyalgia rheumatic and one case of exacerbation of pre-existing asthma.

ZEST:

The safety profile of ZOSTAVAX in the ZEST was comparable with that observed in the SPS. Among the 11,184 subjects who received one dose of ZOSTAVAX, the most frequently reported adverse events were transient local reactions. One case of an anaphylactic reaction was reported and considered vaccine-related.

There were more cases of varicella or zoster-like rashes in the 42 days following the injection in the vaccinated group (69 cases of varicelliform rash in the ZOSTAVAX group versus 55 cases in the placebo group and 19 of zoster rash in the ZOSTAVAX group versus 15 in the placebo group). The vaccine strain of VZV was not detected in any of the 47 samples available and analysed by PCR.

Other studies:

The safety profile of ZOSTAVAX observed in other clinical studies was similar to that observed in the SPS and ZEST with a predominance of local adverse events and headaches.

9.2.2 Pharmacovigilance data

Analysis of observational studies data and international pharmacovigilance data obtained after 8 years on the market and approximately 16 million doses sold has not revealed any new pharmacovigilance signals for this proprietary medicinal product.

09.3 Summary & discussion

ZOSTAVAX is the first vaccine indicated for the prevention of zoster and post-herpetic neuralgia (PHN) in subjects aged 50 and over. It is a live attenuated vaccine against VZV produced using the OKA strain.

The available efficacy data for the ZOSTAVAX vaccine (see Table 4) rely mainly on subjective criteria which makes them difficult to interpret and transpose. Furthermore, the choice of primary efficacy endpoint in the SPS appears questionable; demonstration of the effect of this vaccine on zoster incidence (secondary endpoint) would have been a more relevant endpoint.

These data demonstrate that the protective efficacy of ZOSTAVAX against zoster decreases with increasing age at vaccination: 69.8% (95% CI [54.1%; 80.6%]; $p < 0.001$) in adults aged 50 to 59 and 51.3% (95% CI [44.2%; 57.6%]; $p < 0.001$) in adults aged 60 and over.

The observational studies, with their limitations in terms of method and transposability to France, demonstrate similar results for zoster incidence.

Table 4: Summary of the efficacy results of the SPS, STPS, LTPS and ZEST

| Study (type) | Population (Mean age at inclusion) | Study duration (Time post-vaccination) | Numbers | | Efficacy* | | |
|------------------|------------------------------------|--|----------|---------|--------------------|---------------------------|------------------------------|
| | | | ZOSTAVAX | Placebo | BOI score [95% CI] | Incidence of PHN [95% CI] | Incidence of zoster [95% CI] |
| ZEST (phase III) | 50-59 years (54.8 years) | 2 years (0 to 2 years) | 11,211 | 11,228 | | | 70% [54; 81] |
| SPS (phase III) | ≥ 60 years (69.4 years) | 4.9 years (0 to 4 years) | 19,270 | 19,276 | 61% [51; 69] | 67% [48; 79] | 51% [44; 58] |
| STPS (follow-up) | (73.3 years) | 2.2 years (4 to 7 years) | 7320 | 6950 | 50% [14; 71] | 60% [-10; 87] | 40% [18; 56] |
| LTPS (follow-up) | (74.5 years) | 4.7 years (7 to 10 years) | 6867 | - | 37% [27; 46] | 35% [9; 56] | 21% [11; 30] |

* The efficacy of the vaccine is defined as the percentage reduction in the endpoint evaluated or its incidence compared with the comparator group (placebo).

Moreover, the efficacy of ZOSTAVAX seems to decrease over time and the need for repeated boosters to extend individual protection has not been established. Therefore there might be a potential risk of zoster occurring at a more advanced age in frailer individuals for whom the complications of the disease are more frequent and more severe.

Despite a high frequency of local reactions, the safety profile of ZOSTAVAX live attenuated vaccine is satisfactory overall.

010 THERAPEUTIC USE

According to the HCSP opinion,² vaccination against zoster with the ZOSTAVAX vaccine is recommended in adults aged 65 to 74 years with a one-dose vaccination regimen.

During the first year after the inclusion of the vaccine in the vaccination calendar, individuals aged 75 to 79 years can also be vaccinated.

In view of all the above data and information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

- ▶ Zoster is a disease with potentially serious complications (post-herpetic neuralgia, eye involvement, etc.).
- ▶ This proprietary medicinal product is intended as preventive therapy.
- ▶ The efficacy/adverse effects ratio is modest.
- ▶ There is no vaccination alternative.

- ▶ **Public health benefit:**

Although not life-threatening, the public health burden of zoster and post-herpetic neuralgia (PHN) can be considered moderate due to the high incidence of zoster in the general population, increasing rapidly with age, and its severe repercussions on the quality of life of patients and the resulting economic consequences.³⁰

According to the sentinel network, the annual incidence of zoster in France in 2012 was estimated at 4.4 – 5.2 new cases per 1000 in the general population. The highest incidence concerns individuals aged 70 to 80 years with 12 cases per 1000 [9 - 15],¹¹ which would represent more than 60,000 cases annually in this age group.³¹ The burden of illness in the younger populations concerned by the HCSP vaccination recommendations is accordingly low.

A reduction in the incidence of zoster and PHN does not constitute a public health need within the established framework of priorities. However, vaccination against zoster is now recommended in some populations (HCSP recommendations²).

Vaccination against zoster can help to reduce the public health burden of the illness, in conjunction with current therapeutic measures (early antiviral treatment). However, unlike the majority of vaccines, ZOSTAVAX is not expected to have a protective effect on unvaccinated subjects.

Considering the data on vaccination efficacy obtained from the SPS in subjects aged 60 and over of an incidence of zoster of 51.3%, 95% CI [44.2; 57.6] (i.e. an absolute reduction of 5.7 cases of zoster per 1000 person-years) and a 39% reduction in the incidence of PHN, 95% CI [7; 59] in subjects who have had zoster, the impact of ZOSTAVAX on the reduction in VZV-related morbidity is considered to be low. The protective efficacy in terms of zoster prevention is lower in subjects aged 70 and over than in subjects aged 60 to 69 years while the protective efficacy in terms of PHN prevention in cases of zoster seems limited to subjects aged 70 to 79 years.

Furthermore, vaccination efficacy diminishes significantly over time (the STPS and LTPS) and zoster prevention becomes uncertain more than 5 years after vaccination.

Moreover, vaccination is not expected to have any benefit on the impact on daily living activities of patients and adverse effects in the form of local reactions are frequently reported.

The transposability of clinical trial data is not guaranteed given uncertainties in relation to:

³⁰ Chidiac C, Bruxelles J, Daures JP, Hoang-Xuan T, Morel P, Leplège A, et al. Characteristics of patients with herpes zoster on presentation to practitioners in France. *Clin Infect Dis*. 2001; 33(1): 62-9.

³¹ Demographic profile 2013. INSEE estimate at 1 January 2014 for 70-80-year-olds in metropolitan France. Available at http://www.insee.fr/fr/themes/detail.asp?ref_id=bilan-demo&page=donnees-detaillees/bilan-demo/pop_age2b.htm.

- the decrease in vaccination efficacy with increasing age at vaccination;
- the decrease in vaccination protection over time and the possible need for a booster at a more advanced age and even during immunosenescence;
- the possibility to postpone zoster to at a more advanced age and the associated consequences (higher risk of PHN, or of decompensation);
- insufficient data available on the efficacy of vaccination against ophthalmic zoster and in very elderly patients or those with an impaired immune status.

The vaccine is thus contraindicated in immunosuppressed individuals and not recommended in very elderly subjects (80 years and over), at the highest risk of having severe forms of zoster. Although real-life data are available in the USA, they do not resolve these uncertainties at this stage.

An impact on treatment organisation could be assumed by reducing hospital admissions associated with zoster, however this impact is little documented at this stage.

Consequently, in the light of the available data, ZOSTAVAX is not expected to have an impact on public health in the populations recommended by the HCSP.

Taking account of:

- **the modest efficacy on zoster incidence in the populations recommended by the HCSP,**
 - **the decrease in vaccination protection with age and over time,**
 - **the contraindication of vaccination in immunocompromised individuals,**
- the Committee considers that the actual benefit of ZOSTAVAX is moderate in the prevention of zoster and post-herpetic neuralgia, in the populations recommended by the HCSP in its opinion of 25 October 2013.**

The Committee gives a favourable opinion as regards inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation and in the populations recommended by the HCSP.

► Proposed reimbursement rate: 30%

011.2 Improvement in actual benefit (IAB)

In view of the available data and the absence of a vaccination alternative, the Committee considers that ZOSTAVAX provides a minor clinical added value level IV) in the prevention of zoster, in the populations recommended by the HCSP.

011.3 Target population

The target population of ZOSTAVAX comprises non-immunosuppressed individuals aged 65 to 74 years in addition to, during the first year after the inclusion of the vaccine in the vaccination calendar, non-immunosuppressed individuals aged 75 to 79 years.

According to INSEE data (2007-2060 population projections for metropolitan France) and National Health Insurance data,³² this population can be estimated at:

1. Individuals aged 65 to 74 years

The number of non-immunosuppressed individuals eligible for vaccination annually at age 65 would be approximately 690,000. For a temporary catch-up period, non-immunosuppressed individuals aged 66 to 74 years, i.e. approximately 4,317,000 adults, could also be vaccinated.

2. Individuals aged 75 to 79 years, during the first year

The number of non-immunosuppressed adults aged 75 to 79 years who could be vaccinated during the first year after the inclusion of the vaccine in the vaccination calendar would be approximately 1,827,000.

After a temporary catch-up period, the target population of ZOSTAVAX will ultimately be approximately **690,000 individuals/year**.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

► Presentations

They are suitable for the conditions for prescription and use.

³² Percentages of immunosuppressed individuals: 65-69 years = 10.4%; 70-74 years = 12.6%; 75-79 years = 13.4% (source: AMELI [National Health Insurance website] – ALD 2012)

Appendix: Opinion of the Haut Conseil de la Santé Publique [French Public Health Council] of 25 October 2013 relating to the vaccination of adults against zoster with the ZOSTAVAX vaccine

Haut
Conseil de la
Santé Publique

Haut Conseil de la Santé Publique

OPINION

relating to the vaccination of adults against zoster
with the Zostavax® vaccine

25 October 2013

The Zostavax® vaccine was granted European Marketing Authorisation on 19 May 2006. It is a live attenuated vaccine produced in human diploid cells (MRC5) from the OKA/Merck strain.

In December 2006, the Conseil supérieur d'hygiène publique de France [French Council for Public Health] (CSHPF), transmissible diseases section, issued an opinion concerning the zoster vaccine [1]. It was considered that, in the current state of knowledge, mass vaccination with the zoster vaccine could not be recommended.

The absence of certain data at the time was a limiting factor.

The proposed vaccine was frozen, its duration of protection was unknown and a correlation had not been demonstrated between the immunity obtained and clinical protection. Moreover, the efficacy of a possible booster after the age of 70 years had not been established and it had been hypothesised that the vaccine might cause zoster to occur at a more advanced age. Finally it had been considered that early treatment of zoster with an antiviral could reduce the duration of pain in the acute phase and subsequent neuralgia.

Some of these questions have been raised in recent years.

This vaccine is currently available in a refrigerated form. The duration of protection is now better understood with a follow-up of more than 7.5 years. The early treatment of zoster with an antiviral would not reduce the incidence of neuropathy, hence the benefit of the vaccine and prevention. Finally, in studies monitoring the vaccinated patient cohort, there seems to be no increase in zoster at a more advanced age.

The HCSP thus initiated its own examination to determine the use of this vaccine within the context of current adult vaccination strategies.

The case for the following recommendations is detailed in the report appended to this opinion.

The HCSP has taken the following into account:

1 – The epidemiology of zoster and post-herpetic neuralgia in France

Zoster is a frequent disorder that particularly affects adults: more than 60% of cases occur after the age of 45 years [2,3]. Persistent neuralgia affects mainly individuals over 50 years old. According to some studies, up to close to 20% of adults who have zoster will have post-herpetic neuralgia (PHN). It can be particularly severe when it occurs in the particular context of an elderly, frail individual with multiple diseases and receiving polymedication. In this context “domino effect” decompensations considerably worsen the impact of this initially local disease. Eye involvement is uncommon but clinically serious, and generates significant costs.

Haut Conseil de la santé publique

This opinion should be circulated in full, without additions or changes.

On account of the increase in the number of elderly individuals in the French population, the number of zoster cases should accordingly increase in parallel in coming years.

The risk factors for some have been clearly identified (age, ethnic origin, etc.), but for others they are less well defined (diabetes, composite criteria, multiple diseases, etc.) and do not explain why some individuals exposed to the same risk factors will not have zoster during their lives. The risk of post-herpetic neuralgia (PHN) occurring and persisting is strongly linked to age and comorbidities, and its burden of illness is consequently great in elderly individuals, with a considerable impact on quality of life. The annual incidence of zoster is estimated to be 3.4-4.4 cases per 1000 individuals in the general population,¹ regardless of zoster history. The highest incidence concerns individuals aged 65 years and over, with an estimated incidence of 8 to 10 cases per 1000 individuals, which represents more than 100,000 cases of zoster annually. Relapses are frequent. It is therefore difficult to define a risk population, other than by age, which can be targeted for selective vaccination.

2 – Data concerning vaccine efficacy [4-6]

The data on vaccine efficacy are from the SPS (Shingles Prevention Study), a multicentre, randomised study versus placebo conducted under double-blind conditions and stratified for age (60-69 years and 70 years and over).

The burden of illness (BOI) has been studied according to three criteria: the incidence of zoster, the incidence of post-herpetic neuralgia (PHN), and the Burden of illness (BOI) score. Efficacy according to the zoster-associated pain severity score was 61.1% (95% CI: 51.1-69.1). The protective efficacy against zoster was 51.3% (95% CI: 44.2; 57.6). Zostavax® reduced the incidence of zoster by 63.9% (95% CI: 55.5; 70.9) in individuals aged 60 to 69 years and by 37.6% (95% CI: 25.0; 48.1) in individuals aged 70 and over.

To study the long-term persistence of vaccine efficacy, a subgroup of individuals from the SPS was monitored in two studies: the STPS (short-term persistence substudy) and the LTPS (long-term persistence substudy). The data on protection persistence show that vaccine efficacy diminishes over time, but persists for close to 10 years:

| Age group | % reduction in zoster incidence (95% CI*) | % reduction in “BOI” (95% CI*) | % reduction in PHN incidence (95% CI*) |
|---|---|--------------------------------|--|
| Data from the SPS pivotal study (approximately 3 years of follow-up) | | | |
| All patients | 51.3 (44.2-55.6) | 61.1 (51.1-69.1) | 66.5 (47.5-79.2) |
| 60-69 years | 63.9 (55.5-70.9) | 65.5 (51.5-75.5) | 65.7 (20.4-86.7) |
| 70 years and over | 37.6 (25.0-48.1) | 55.4 (39.9-66.9) | 66.8 (43.3-81.3) |
| Data from the LTPS (after 10 years of follow-up) | | | |
| 60-69 years | 20.2 (6.7-32.2) | 32.5 (16.6-45.4) | 17.1 (-31.0-50.9) |
| 70 years and over | 22.4 (6.0-36.6) | 42.5 (27.5-54.4) | 49.7 (15.6-72.5) |

*CI = 95% confidence interval

¹ Source: Sentinelles network <http://www.sentiweb.org/>.

3 – Data concerning safety

The main safety data are from the SPS pivotal study. The adverse events commonly reported concern mainly reactions at the injection site and headaches. Following analysis of the available data on the reactogenicity of Zostavax® in adults aged 60 and over, the safety of use profile of this vaccine appears satisfactory and remains close to that defined at the time its Marketing Authorisation was granted.

4 – Pharmacovigilance data

Analysis of pharmacovigilance data gathered for more than 13.6 million doses sold over the 6.5 years that it has been marketed worldwide has revealed no particular signals, with a reporting rate of post-vaccination adverse effects of approximately 85/100,000 vaccine doses and 5.2 serious adverse effects/100,000 (zoster-like eruption, pain, rash and fever).

5 – Estimated cost-efficacy ratio

The most cost-effective vaccination strategy is the vaccination of individuals aged 70 years. The probabilistic sensitivity analysis for the model using data from the LTPS shows that 100% of simulations are under the threshold of €50,000/QALY gained and 30% are under the threshold of €30,000/QALY gained. Vaccination at 65 or 75 years of age yields very similar results. The parameters that most influence the results are essentially duration of vaccine protection and, to a lesser extent, vaccine price and zoster incidence. A vaccination strategy against zoster and its associated complications in immunocompetent individuals aged 65 and over, with a subsequent catch-up phase up to 74 years, appears justified from a health economic point of view. The analysis could not be extended to individuals aged 76 to 79 years in the absence of sufficient data concerning the efficacy and duration of protection conferred by vaccination in this age group.

Overall, the HCSP considers that the zoster vaccine has proved to be able to significantly reduce the severity of the disease, i.e. the intensity of post-herpetic neuralgia (61.1%), its incidence (66.5%) and the incidence of zoster (51.3%).

Taking into account the safety data available to date, the safety of use profile of this vaccine remains satisfactory. Furthermore, no satisfactory preventive or therapeutic alternative is currently available.

The cost-effectiveness ratio appears acceptable in relation to the generally accepted thresholds. Taking into account the burden of illness and better vaccination efficacy in younger individuals, the choice is to vaccinate from the age of 65 years.

The HCSP consequently recommends vaccination against zoster in adults aged 65 to 74 years, with a one-dose vaccination regimen. During the first year after the inclusion of the vaccine in the vaccination calendar, individuals aged 75 to 79 years can be vaccinated as part of a catch-up phase.

This live vaccine consisting of an attenuated viral strain of the varicella zoster virus is contraindicated in immunosuppressed individuals.

The need for a booster dose is currently unknown.

The Comité technique des vaccinations [Technical vaccinations committee] (CTV) met on 14 October 2013: 15 out of 17 qualified voting members were present, 0 conflicts of interest, the proposal was approved by 15 voting members, 0 abstentions, 0 against.

The Commission spécialisée maladies transmissibles [Communicable diseases specialist committee] (CSMT) met on 25 October 2013: 10 out of 14 qualified voting members were present, 0 conflicts of interest, the proposal was approved by 10 voting members, 0 abstentions, 0 against

References

- [1] Conseil supérieur d'hygiène publique de France. Avis du 22 septembre 2006 et du 5 décembre 2006 relatif au vaccin contre le zona [Opinion of 22 September 2006 and 5 December 2006 relating to the zoster vaccine].
- [2] Oxman MN, Levin MJ, Johnson GR, *et al.* A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 2005; 352: 2271-84.
- [3] Frazer IH, Levin MJ, Paradigm shifting vaccines: prophylactic vaccines against latent varicella-zoster virus infection and against HPV-associated cancer. *Curr Opin Virol.* 2011 Oct; 1(4): 268-79.
- [4] Zostavax: EPAR Product Information (Marketing Authorisation variation decision date 13.02.13). Available at http://www.ema.europa.eu/docs/fr_FR/document_library/EPAR_Product_Information/human/000674/WC500053462.pdf (consulted on 6/09/2013).
- [5] Zostavax: EPAR – Scientific discussion Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Scientific_Discussion/human/000674/WC500053460.pdf (consulted on 6/09/2013).
- [6] Schmader KE, Levin MJ, Gnann JW, *et al.* Efficacy, Safety, and Tolerability of Herpes Zoster Vaccine in Persons Aged 50-59 Years. *Clin Infect Dis* 2012; 54: 922-28.

Opinion delivered by the CSMT, at the proposal of the CTV
25 October 2013

Haut Conseil de la santé publique

14 avenue Duquesne
75350 Paris 07 SP
www.hcsp.fr