EUnetHTA WP5 Joint Action 2 Strand A, Rapid Relative Effectiveness Assessment of pharmaceuticals

ZOSTAVAX FOR THE PREVENTION OF HERPES ZOSTER AND POSTHERPETIC NEURALGIA

Pilot assessment using the draft HTA Core Model for Rapid Relative Effectiveness Assessment

Pilot ID: WP-SA-1

V4.0 Final version, September 2013

Document history

Version	Date	Description
V1.0	22 May 2013	First draft
V2.0	26 June 2013	Second draft Input from dedicated reviewers has been processed.
V3.0	6 September 2013	Third draft Input from MAH and WP5 members has been processed.
V4.0	17 September 2013	Final version Input from medical editor has been processed.

This assessment was produced by experts from the institutions listed below, and was reviewed by members of Work Package 5 (WP5) Joint Action 2 of the EUnetHTA network; the whole process was coordinated by the Dutch Health Care Insurance Board (CVZ).

The model represents a consolidated view of the non-binding recommendations of the EUnetHTA network members and is in no case the official opinion of the participating institutions or individuals.

Authoring agency:	CVZ: Health Care Insurance Board (the Netherlands)
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Dedicated reviewing agencies:	HAS: French National Authority for Health (France)
	DPA/MHEC: Directorate for Pharmaceutical Affairs, Ministry for Health, the Elderly and Community Care (Malta)
	RIZIV-INAMI: National Institute for Health and Disability Insurance & KCE: Belgian Health Care Knowledge Centre (Belgium)
	BIQG/GÖG: The Health Austria GmbH (Austria)
	MoH Cz Rep: Ministry of Health of the Czech Republic (Czech Republic)
	Regione Veneto (Italy)
	DGCF MSSSI: Ministry of Health, Social Policy and Equality, Directorate General for Pharmacy and Healthcare Products (Spain)

Involvement of stakeholder: Marketing Authorisation Holder (MAH) - Sanofi Pasteur MSD (SPMSD).

MAH indicated willingness to participate in this pilot by submitting an expression of interest. The draft REA submission file provided by the company was the basic documentation for the assessment. There was a face-to-face scoping meeting of representatives of the authoring agency, co-authoring organisation and the MAH. After the face-to-face scoping meeting the authors sent their feedback on the draft submission file to the MAH. The final submission file from the company was received on 12 April 2013 and this document constituted an incentive for authors to finalise the Project Plan and plan timelines. Publications from the reference list of the submission file were received on 25 April 2013. The consultation with the MAH included the scoping document, timelines and second draft of the pilot assessment.

Conflict of interest:

Work package 5, Strand A members who expressed interest in participation in the Zostavax pilot completed declarations of conflict of interest (CoI). Declarations were collected by the coordination team of the pilot between 28 February and 6 March 2013. Two participants were further excluded from the process based on the potential CoI declared in their statements. All other authors and reviewers involved in the production of this pilot assessment have declared that they have no actual or potential CoI and based on this declaration could obtain access to confidential material. The final submission file was shared with the authors of the Zostavax pilot on 12 April and with reviewers on 22 May, 2013.

At the beginning of the pilot process, the coordination team of the pilot was aware of the existence of a Belgian national assessment of Zostavax report (report of the Commission for Reimbursement of Pharmaceuticals, INAMI-RIZIV, 26 January 2010) in the production of which the Belgian group of reviewers had been involved.

However, the coordination team was not aware that one of the Zostavax pilot reviewers was also an author of the article "Doeltreffendheid van het zonavaccin bij zestigplussers" in a Belgian journal (Minerva: Tijdschrift voor Evidence-Based Medicine; 12 (5)) that was published in June 2013 during the review process of the pilot report. This article was submitted for publication (28 March, 2013) before reviewing process of the Zostavax pilot began (22 May, 2013) and was based on a publicly available Cochrane review (Gagliardi AMZ, Gomes Silva BN, et al. Vaccines for preventing herpes zoster in older adults. Cochrane Database Syst Rev 2012:CD008858).

The coordination team has no indication that confidential information included in the submission file was used in the published article because the aforementioned article was submitted to the journal before the final submission file of the MAH was available to Zostavax pilot reviewers. However, the coordination team is of the opinion that the reviewer-author of the journal article should have informed the coordination team in advance that he was working on a manuscript for the aforementioned article that could be published while the pilot process was underway. This note is so intended to ensure that the readers of the report are aware of the publication of this article during this pilot assessment. The views expressed in the aforementioned publication solely represent the views of the authors of the article, including the reviewer in question. The article is not a part of the present assessment.

Table of contents

SUMMARY OF RELATIVE EFFECTIVENESS OF ZOSTAVAX

The assessment element ID codes in brackets (e.g. A0001) refer to the result cards in Appendix 1, which give details of the relevant results.

Scope

Population	Immunocompetent individuals of 50 years or older. Subgroup analyses for age ranges including 50-59 years, 60-69 years, 70-79 years, ≥70 years and ≥80 years.
Intervention	Zostavax®, a varicella zoster virus (VZV) vaccine for the prevention of herpes zoster ('zoster' or shingles) and herpes zoster related post-herpetic neuralgia.
Comparator	Placebo
Outcomes	1. Incidence of herpes zoster (HZ) and incidence of post herpetic neuralgia (PHN). 2. Survival data, such as overall survival or progression free survival. 3. Burden of illness (BOI), severity and duration of the pain, hospitalisation, health-related quality of life (HRQL) and activities of daily living.

Introduction

Health problem

Herpes zoster (HZ), commonly known as shingles, can only occur in people who have had an infection with varicella zoster virus, commonly known as chicken pox. The risk of developing HZ increases with age, in particular in people over 50 years old. Of those aged 85 years, 50% have experienced HZ. Reactivation of varicella zoster virus (VZV) is associated with the age-related decline in cell-mediated immunity and therefore occurs more frequently in older adults. Other risk factors for HZ are immunosuppression (such as human immunodeficiency virus [HIV] infection) and tumours *(A0003)*.

HZ is clinically characterised by rash and pain. The most frequently debilitating symptom is neuropathic pain which may occur during three phases of HZ: acute herpetic neuralgia, subacute herpetic neuralgia, and post-herpetic neuralgia (PHN). The acute phase of HZ is characterised by a unilateral and vesicular rash that lasts up to 4 weeks, most often accompanied by pain or discomfort. The subacute herpetic phase refers to pain that persists beyond the healing of the rash, and persists from 30 days to several months after the initial onset of the rash. Finally, PHN is the phase of chronic pain and refers to pain persisting beyond 3-4 months from the initial onset of the rash. It can last for many years *(A0002-A0005-A0004)*.

Important elements in establishing the diagnosis include: 1) painful or abnormal sensory prodrome; 2) dermatomal distribution; 3) grouped vesicles; 4) multiple sites filling the dermatome, especially where divisions of the sensory nerve are represented; 5) lack of history of a similar rash in the same distribution (to rule out recurrent zosteriform herpes simplex); and 6) pain and allodynia in the area of the rash. One element that helps the diagnosis of HZ is the patient's previous exposure to VZV *(A0024)*.

Diagnosis of HZ in the prodromal period can be extremely difficult. The diagnosis can be facilitated by the appearance of the rash and by questioning the patient about their clinical history. If the rash does not occur, it is very difficult to diagnose the disease because HZ presents symptoms similar to those of other diseases *(A0024)*.

An overall annual incidence of HZ of 2.0-4.6 cases per 1000 people has been estimated in Europe. It is highly age dependent. HZ incidence rates appeared to increase rapidly after 50 years to around 7–8/1000 up to 10/1000 at 80 years of age and older. Country-specific incidence estimates (for Belgium, France, Germany, Iceland, Italy, the Netherlands, Spain, Switzerland and UK) are reported *(A0006)*.

Data on HZ mortality are limited but suggest that fatal cases are likely to be rare especially among immunocompetent healthy people. HZ is rarely recorded as the cause of death in patients under 65 years old ***(A0006).***

HZ and PHN have a negative impact on the physical, psychological, functional and social status of patients. Pain is one of the main symptoms of PHN and has, both for HZ and PHN, a strong impact on perceived quality of life. Pain and anxiety are the dimensions of EQ-5D that are most affected by HZ ***(A0005)***.

In 2012 the potential Zostavax target population (persons at least 50 years old) in the 27 EU countries[a] amounted to a total of 188 million people ***(A0023)***.

Due to the lack of preventive measures for HZ apart from Zostavax, there is no joint guideline for the EU dealing with the prevention of HZ, but some national guidelines exist worldwide. In 2008, the Advisory Committee on Immunization Practices (ACIP) in the United States of America (USA) recommended the use of a live attenuated vaccine in people aged 60 years old or older for the prevention of HZ and its sequelae. No similar recommendation is available for Europe at the moment. On the other hand, various guidelines dealing with the treatment of HZ (once its symptoms are noticed) are available. Treatment guidelines recommend the use of oral antiviral agents for the treatment of HZ. Treatment can be effective if it is started within 72 hours of the onset of acute symptoms. In a few cases therapy is started more than 72 hours after the onset of acute symptoms because the patient delays the medical visit or because the often unusual symptoms have made diagnosis difficult for the physician. The management of patients with PHN is very difficult. The oral antiviral agent can reduce the duration and severity of pain, but it cannot prevent the onset of PHN ***(A0025)***.

Substantial differences in HZ management (treatment) exist in the different European countries. Official guidelines for HZ treatment are still lacking for many countries. Austria refers to the German guidelines. The German guideline identifies systemic antiviral therapy as first choice. ***(A0025)***.

Description of technology

Zostavax is a lyophilised preparation of live, attenuated vaccine containing VZV (Oka/Merck strain). Each dose (0.65 ml) contains not less than 19,400 plaque forming units (PFU) of VZV. Zostavax contains the same strain as used in vaccines to prevent varicella (the primary infection of VZV) but at a higher potency.

Zostavax was first authorised in Australia on 2 May 2006 (International Birth Date). The vaccine was authorised in the EU on 19 May 2006 and in the USA on 25 May 2006 and the first launch worldwide was in the USA in June 2006. In Europe, market authorisation is granted for the refrigerated formulation whereas in the clinical studies the frozen formulation was mostly used ***(A0020)***.

Zostavax is indicated for prevention of HZ and HZ-related PHN. It is indicated for immunisation of people aged 50 years or older.

The groups not eligible for vaccination are those ***(A0007)***:

- with hypersensitivity to the active substance, or to any of the excipients or trace residuals (e.g. neomycin)
- with 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
- undergoing immunosuppressive therapy (including high-dose corticosteroids); however, Zostavax is not contraindicated for individuals receiving topical or inhaled corticosteroids, or low-dose systemic corticosteroids, or patients who are receiving corticosteroids as replacement therapy (e.g. for adrenal insufficiency)

[a] On 1 July 2013 Croatia became the 28th member of the European Union. In this assessment information about Croatia are not incorporated.

- with active untreated tuberculosis
- who are pregnant.

Zostavax vaccine is available as a powder and solvent to be made up into a suspension for injection. It is given as a single dose of 0.65 ml injected subcutaneously in the deltoid region of the upper arm. The present approved potency and formulation of Zostavax differ from the ones studied in clinical trials ***(B0001)***.

Placebo is the comparator in the clinical trials ***(B0002)***.

Real and long-term sustainable production capabilities for Zostavax represented a critical issue in the past. OKA/Merck strain declared improvements and investments in the production processes which should allow a better supply of Zostavax worldwide ***(B0003)***.

Long-term safety will be monitored through the obligatory updates of the registration authorities (e.g. the Periodic Safety Update Reports and the Vaccine Event Reporting System) ***(C0004)***.

Results

Available evidence

The safety and clinical effectiveness of Zostavax has been investigated in several clinical studies.[b] The first pivotal randomised controlled trial (RCT) is the Shingles Prevention Study (SPS), which enrolled 38,546 participants aged 60 years or older (intervention group: 19,270, placebo group: 19,276 participants; intention to treat population). A substudy of the SPS (Adverse Event Substudy) involving 6616 participants within the SPS cohort (intervention group 3345 participants and placebo group 3271 participants) has also been conducted for further evaluation of adverse events. Mean follow-up of the SPS is 3.1 years. The second RCT is the Zostavax Efficacy and Safety Trial (ZEST), which included 22,439 participants aged 50-59 years (intervention group: 11,211 participants, placebo group: 11,228 participants; intention to treat population). Mean follow-up was 1.3 years. Participants with a contraindication were excluded from the studies.

The primary efficacy outcome of the SPS is vaccine efficacy for the burden of illness (BOI), a composite endpoint affected by the incidence, severity and duration of the associated pain and discomfort. The primary outcome of the ZEST is incidence of HZ. Secondary endpoints in the SPS is the incidence of PHN and for the ZEST antibody titer and safety.

In this assessment, we have separated the individual parameters of the vaccine efficacy for BOI and presented them according to age group. Data for the incidence of HZ, the incidence of PHN, mortality, hospitalisation rate, pain, activities of daily life, health related quality of life and adverse events, were reported.

Upcoming evidence

Twelve ongoing studies are outlined in Appendix 1, Table 3.

Safety

In immunocompetent participants aged 50 years or older, a single dose of Zostavax has a low-risk safety profile. The most common side effect observed is a reaction at the injection site ***(C0001A)***. As compared to the placebo group, HZ vaccine leads to more adverse events. In the two clinical trials, the overall incidences of vaccine-related injection-site adverse reactions were 17% and 14% in the placebo groups versus 48% and 64% in the vaccine groups. The vaccine group also had more vaccine-related systemic adverse events ***(C0001B1)***.

Age is a risk factor for severe adverse events. In both study arms (Zostavax and placebo), the number of participants with 1 or more severe adverse events increases with

[b] For full characteristics of the pivotal studies: see table 1 of appendix 1. For details of the published studies on the clinical development of Zostavax: see appendix 4.

age *(C0001B2)*. This increase is even greater in the Zostavax group. Vaccinees aged 80 years or older are more than twice as likely to have severe adverse events after Zostavax vaccination compared with the placebo group *(C0005)*.

Clinical effectiveness

The SPS and ZEST studies show that, compared with placebo, a single dose of Zostavax effectively decreases the incidence of HZ in immunocompetent people aged 50 years or older *(D0006)*. Vaccine efficacy (on average over 50%) is age dependent: participants aged 50-59 years benefit the most (72%), followed by those aged 60-69 years (64%), and 70-79 years (41%), and in the oldest age group (80 years or older) vaccine efficacy is lowest (18%) *(D0011C)*. Data from three retrospective real life studies with patients who were vaccinated with Zostavax seem to show comparable decreases in the incidence of HZ after vaccination. However, insurance databases were used for these studies and it is not totally clear from the publications how reliable the results for vaccine efficacy are. *(D0017)*.

The incidence of PHN is also lower after vaccination with Zostavax compared with placebo. The vaccine efficacy for PHN is on average 67% among the total study population of persons aged 60 years or older. A possible age-related effect is less obvious; a correlation between the Zostavax and placebo group could not be shown. *(D0006)*.

The effect on PHN seems to be related to the decreased incidence of HZ, because HZ is a prerequisite for the occurrence of PHN. If only those participants who developed HZ after vaccination are taken into account, the vaccine efficacy for PHN is lowered to 39% on average *(D0006)*. In this case the vaccine efficacies for PHN are: 5% for those aged 60-69 years, 55% for those aged 70-79 years and 26% for those aged 80 years or more *(D0011C)*.

Vaccination with Zostavax did not reduce mortality *(D0001)* and hospitalisation rates *(D0011D)* due to HZ/PHN. Also, an improvement of HRQL in vaccinees who developed HZ can not be demonstrated *(D00012 and D00013)*. There is insufficient evidence to determine whether pain and activities of daily living are influenced by Zostavax *(D0005 and D0016)*.

Reimbursement

The reimbursement/funding of the HZ vaccine is decided at country level and some differences are observed within Europe according to the healthcare system of the country. Details at country level are reported in *A0021*.

Summary of relative effectiveness of Zostavax (frozen formulation) versus placebo for the prevention of herpes zoster, HZ-related post-herpetic neuralgia and adversed events in people aged 50 years or older in SPS (including substudy) and ZEST

Age group [years]	Nz/Np (mITT)	**Health benefit** *(D0001, D0002B, D0005, D0006, D0011A, D0011C)*					**Harm** *(C0001B1, C0001B2)*	
		Vaccine Efficacy† for incidence of HZ	**Vaccine Efficacy† for incidence of PHN** in total study population	**Vaccine Efficacy† for incidence of PHN** in those who develop HZ after vaccination	**Mortality: difference in risk**	**Vaccine Efficacy† for BOI**	**Severe AEs (Grade 3-4); Subjects with at least 1 SAE. Relative Risk**	**Frequent AEs of any severity grade**
50-59	11,165/11,189	**72%** (57; 83)[1]	n.a.	n.a.	**0.0%** (0.0 to 0.0)[1]	∫**73%** (53 to 85)[1]	n.a. #**1.1** (0.9 to 1.3)[1]	**64%** (Zostavax) versus **14%** (placebo)[1]
≥ 60	19,245/19,247	**51%** (44 to 58)[2]	**67%** (48 to 79) [3] &**69%** (46 to 58) [4]	**39%** (7 to 59)[2] &**36%** (-9 to 62) [4]	**0.0%** (-1.2 to 1.2)[3]	**61%** (51 to 69)[3]	**1.0** (0.9 to 1.2)[2] #**1.5** (1.0 to 2.3)[2]	**48%** (Zostavax) versus **17%** (placebo)[5]
60-69	10,370/10,356	**64%** (56 to 71)[2]	**66%** (20 to 87)[3]	**5%** (-107 to 56)[2]	**-0.8%** (-2.0 to 0.4)[3]	**66%** (52 to 76)[3]	**1.1** (0.9 to 1.5)[2] #**1.2** (0.7 to 2.2)[2]	n.a.
≥70	8,884/8,891	**38%** (25 to 48)[3]	**67%** (43 to 81)[3]	**47%** (13 to 67) [6]	**1.0%** (-1.2 to 3.1)[3]	**55%** (40 to 67)[3]	n.a. #n.a.	n.a.
70-79	7,621/7,759	**41%** (28 to 52)[2]	**74%** (49 to 87)[7]	**55%** (18 to 76)[2]	n.a.	**59%** (43 to 71)[7]	**0.9** (0.7 to 1.1)[2] #**1.6** (0.9 to 2.8)[2]	n.a.
≥80	1,263/1,332	**18%** (-29 to 48)[2]	**40%** (<0 to 67)[7]	**26%** (-69 to 68)[2]	n.a.	**38%** (<0 to 67)[7]	**1.4** (0.8 to 2.4)[2] #**2.2** (0.8 to 6.5)[2]	n.a.
Quality of body of evidence *		High	High	Moderate	High	Low	Moderate	High

Data are presented as percentages with 95% confidence intervals (CI) in parentheses. No 95%CIs were available for the frequency data in the last column.

Abbreviations: **Nz**=number of participants vaccinated with Zostavax; **Np**=number of participants injected with placebo; **mITT**=modified intention-to-treat; **BOI**=burden of illness; **AE**=adverse event; **n.a.**=no data available; **HZ**= Herpes zoster; **PHN**= Post-herpetic neuralgia; **SPS**= Shingles Prevention Study; **ZEST**= Zoster Efficacy and Safety Trial.

Note: The number of participants included into a safety analysis in FDA publication[2], is slightly different from the numbers reported in pivotal studies.

† Percentage reduction compared with placebo group.

∫ BOI in 50-59 is calculated over a 21-day period following HZ rash onset (whereas in 60 years or older, BOI is calculated over 182 day-period).

SPS adverse events substudy

& Results are based on the more strict selection of PNH cases (persisting or recurring pain more than 120 days instead of 90 days) in the Cochrane Study of Chen et al.[4] Vaccine efficacy (%) was calculated as 100*(1-Risk Ratio) as was reported in the Chen Cochrane Study[4]

* High = We are very confident that the true effect lies close to that of the estimate of the effect; Moderate = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;

Discussion

Both clinical studies discussed in this assessment (SPS and ZEST) are well-designed RCTs. In both trials the total number of participants in the two cohorts was sufficient to assess possible difference in the incidence of HZ. However, because the incidence of PHN is lower, the number of confirmed cases of PHN in the studies was low. Further, because of its particularly low incidence in participants aged 50-59 years old, the incidence of PHN was not studied in this age group. This issue may need an even bigger population or a different study design, e.g. a cohort entirely of patients with HZ, to reach conclusions about the effect of Zostavax in the prevention of PHN.

Other relevant limitations of the results are:

- After initial registration, the formulation of Zostavax was changed from a frozen one to a refrigerated one. Although the bridging study, as required by the EMA, showed comparable VZV antibody geometric mean titres in the two formulations, the effect of the refrigerated formulation on relevant outcomes, such as prevention of HZ or PHN, has not been studied.
- Individuals with compromised immunity were excluded from the studies (contraindication). There is limited information about the effectiveness of Zostavax in this group, who may need a preventive vaccine the most.
- People who have been vaccinated can later become immunocompromised, as a result of senescence, disease or medication. It is not clear whether such people will be more susceptible to reactivation of VZV.
- The primary endpoint in SPS (vaccine efficacy for BOI) is a composite endpoint. Composite endpoints are multifactorial, difficult to interpret and their incorrect interpretation may result in an overestimation of the effects of an intervention. It is also possible that the calculated effect results from multiplying artifacts. Analysis of the individual parameters separately is a partial solution to this problem.
- Pain control and improved quality of life are important for affected patients. The methods of pain assessment in the clinical trials are questionable. In addition to the methodological limitations of the studies, the clinical relevance of the measured outcome parameters is not certain.
- The oldest age group is most vulnerable, but the oldest elderly (participants aged 80 years of older), was not a prespecified subgroup in the studies. The posthoc analysis of this relatively small subgroup entails uncertainties.

Long-term data about safety and efficacy after 10 years is lacking. Therefore, the relevance of an eventual revaccination cannot be assessed within the remit of this report.

Conclusion

Zostavax administered as a single dose in immunocompetent people aged 50 years or older is more effective in preventing HZ than is placebo. This incidence lowering effect decreases with increasing age. Beyond the prevention of HZ, there may be an effect on the prevention of PHN by Zostavax in certain age groups (70-79 years). More data are required to demonstrate this conclusively. No significant effect can be shown on mortality, hospitalisation rate and HRQL. Due to limitations of the methodology used, the effect of Zostavax on activities of daily living and pain reduction is not clear.

A single dose of Zostavax in immunocompetent people aged 50 years or older has a similar safety profile compared with placebo. Subgroup analysis showed that age is a risk factor for severe adverse events. Participants aged 80 years or older were at greatest risk. However, because this age group was not a predefined age stratum, further investigations are needed to determine the risk profile in the oldest elderly.

People with compromised immunity are excluded from the clinical trials, so limited data about the efficacy of Zostavax in this group is available. Long-term data (beyond 10 years) about efficacy and safety is lacking. Therefore, the relevance of an eventual revaccination cannot be assessed within the remit of this report.

LIST OF ABBREVIATIONS

Ab	Antibody
ACIP	Advisory Committee on Immunization Practices
ADL	Activity of daily living
ADLI	Activities of daily living interference
AE	Adverse event
AIFA	Italian Medicines Agency
AUC	Area under the curve
BOI	Burden of illness
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CVZ	Dutch Health Care Insurance Board
ELISPOT	enzyme-linked immunosorbent spot
EMA	European Medicines Agency
EPAR	European public assessment report
FDA	Food and Drug Administration
FUM	Follow-up measures
GMFR	Geometric mean fold rise
GMT	Geometric mean titre
gpELISA	glycoprotein enzyme-linked immunosorbent assay
HAART	Highly active anti-retroviral therapy
HAS	Haute Autoritè de Santè
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQL	Health related quality of life
HSV	Herpes simplex virus
HTA	Health technology assessment
HZ	Herpes zoster
HZO	Herpes zoster ophthalmicus
IFN-gamma	Interferon-gamma
IQWIG	German Institute for Quality and Efficiency in Health Care
ITT	Intention to treat
KCE	Belgian Healthcare Knowledge Centre
MAH	Marketing authorisation holder
MCS	Mental component summary
mITT	Modified intent-to-treat
NCT	Clinical Trial Registry number
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence (UK)
NNT	Number needed to treat
NNTB	Number needed to treat to benefit
NNTH	Number needed to treat to harm
NNV	Number needed to vaccinate
PBAC	Australian Government, Department of Health and Ageing, Pharmaceutical Benefit Advisory Committee
PCS	Physical component summary
PFU	Plaque forming units
PHN	Post-herpetic neuralgia
PICO	Patient problem, intervention, comparison, outcome
RCT	Randomised controlled trial
RD	Risk difference
REA	Relative effectiveness assessment
RMP	Risk management plan
RR	Relative risk or risk ratio
SAE	Severe adverse event

SF-12	12-Item short-form health survey
SPC	Summary of product characteristics
SPMSD	Sanofi Pasteur MSD
SPS	Shingles Prevention Study
VAERS	Vaccine adverse event reporting system
VAS	Visual analogue scale
VZV	Varicella zoster virus
WP	Work package
ZBPI	Zoster brief pain inventory
ZEST	Zoster Efficacy and Safety Trial
ZV	Zoster vaccine

1 SCOPE

Description	Project scope; PICO
Population	Health condition: herpes zoster (HZ; 'zoster' or shingles) and HZ-related post-herpetic neuralgia (PHN). ICD-10 codes: B02: zoster (herpes zoster) incl. shingles, zona. B02.2+: zoster with other nervous system involvement. G53.0* postzoster neuralgia (B02.2+). MeSH-terms diseases: "herpes zoster" "neuralgia, postherpetic". *The target population and possible limitation:* Immunocompetent individuals of 50 years or older. Subgroup analyses for age ranges including 50-59 years, 60-69 years, 70-79 years, 70 years or older and 80 years or older. *Intended use of the technology:* For the prevention of HZ ('zoster' of shingles) and HZ- related PHN. For immunisation of individuals 50 years of age or older.
Intervention	Zostavax®: viral vaccine with (live, attenuated) varicella zoster virus (VZV), Oka/Merck strain. Produced in human diploid MRC-5 cells, one dose of 0.65 ml contains not less than 19,400 plaque-forming units (PFU). A single injection (0.65 ml) is given subcutaneously, preferably in the deltoid region. ATC: J07BK02. MeSH-term intervention: "herpes zoster vaccine".
Comparison	Comparator: placebo (injection of 0.5 ml placebo subcutaneously). Rationale: 1) In the clinical trials, 0.5 ml of the vaccine solution was used. 2) At this moment, there is no other intervention aimed at preventing VZV reactivation. Most conventional drugs used are intended as a treatment and not for prevention of HZ or PHN. These treatments include antiviral agents (such as aciclovir), anti-epileptics (pregabalin, gabapentin), tricyclic antidepressants (such as amitriptyline), analgesics including opioids (such as oxycodone, tramadol) and capsaicin cream. MeSH-terms comparator: "placebo".
Outcomes	Outcome for effectiveness: 1. Incidence of HZ and incidence of PHN. 2. Survival data, such as overall survival or progression free survival. 3. Burden of illness (BOI), severity and duration of the pain, hospitalisation, health-related quality of life (HRQL) and activities of daily living.

2 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

2.1 Methods

Domain framing

No deviation was required from the general scope of the project when reporting the results in research questions.

Research questions

Element ID	Research question
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the condition? Who will suffer the most from the condition?
A0004	What is the natural course of the condition?
A0005	What are the symptoms and the burden of disease for the patient? What is the mortality and/or extent of hospitalisation caused by the disease?
A0006	What is the burden of the disease for society? What are the incidence and prevalence of the diseases (HZ and PHN)? What is the mortality due to HZ and PHN?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?
A0024	How is the health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the health condition currently managed according to published guidelines and in practice?
A0020	What is the marketing authorisation status of the technology?
A0021	What is the reimbursement status of the technology?

Sources

- Submission file from MAH
- Assessments from European Medicines Agency and US Food and Drug Administration (FDA)
- Reference databases: Cochrane Central, Centre for Reviews and Dissemination, Medline, Embase, Pubmed
- Guidelines, reference databases, registries and statistics on prevalence, incidence, mortality and morbidity-disability; EUROSTAT database
- For information on funding/reimbursement status: national health services' websites or by direct contact with the agencies.

Analysis

Due to the variety of the issues and the multiple sources of information available only nonsystematic reviewing of the literature and other information sources was feasible, although a systematic review would have been preferred. Descriptive synthesis was used to report the results.

Synthesis

Most of the research questions could be answered in plain text format.

2.2 Main results

HZ and HZ-related PHN are target conditions under assessment. The assessment also covers the mesh terms: ophthalmic HZ or herpes zoster ophthalmicus (HZO).

HZ, or shingles, results from reactivation of the VZV, which has remained latent in the person's sensory ganglia following primary infection i.e. varicella or chickenpox.[51] In a few cases, HZ can be subclinical or exceedingly mild in nature (A0002).

Acute HZ involves VZV replication and spread in the dorsal root or cranial ganglion and peripheral sensory nerve. Local spread may extend to dorsal roots and the spinal cord, and the virus may disseminate via the blood. HZ most commonly localises to the thoracic region followed by the cranial region.[8]

HZ can start with a headache, malaise of varying severity, fatigue, dysesthesia, pruritus and fever. These symptoms are usually followed by sensations of burning, itching, tingling and numbness. The symptoms may precede the HZ eruption (see A0005). As the virus reaches the dermis and epidermis, inflammation and blistering of the skin occur.[8]

HZ is characterised by three phases of acute pain: acute herpetic neuralgia, subacute herpetic neuralgia and PHN.[9]

PHN is the most common debilitating complication of HZ. PHN is a neuropathic pain syndrome, defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system, which persists beyond 3-4 months from the initial onset of the rash and can last for many years. The exact pathophysiology of PHN remains unclear (A0002).[9] Several factors have been consistently identified as influencing the development of chronic pain: older age, greater rash severity and greater acute pain as well as the presence of prodromal pain and impact on functional status.[10]

A strong relationship between pain and activities of daily living (ADL) emerges from the literature.[11]

In clinical studies of Zostavax the Zoster Brief Pain Inventory (ZBPI) was used to calculate an HZ severity-of-illness score[3]. The worst pain score on the ZBPI is correlated strongly with interference with ADL and reduced quality of life.[12]

Diagnosis of HZ in the prodromal period can be extremely difficult. The diagnosis can be facilitated by the appearance of rash and by questioning the patient about their clinical history. If the rash does not occur, it is difficult to diagnose the disease because HZ presents symptoms similar to those of other diseases. The condition that is most commonly mistaken for HZ is herpes simplex virus infection (see A0024).[13]

Criteria followed in the Shingles Prevention Study (SPS)[3] appear to be uncommon in real clinical practice. DNA is not always extracted from clinical specimens obtained from participants suspected of having HZ.

Recent studies conducted in Europe estimate an overall annual incidence of HZ of 2.0-4.6 cases per 1000 persons[14]. The incidence is highly age dependent. HZ incidence rates appeared to increase rapidly after 50 years to around 7–8/1000 up to 10/1000 at 80 years of age and older. Country-specific incidence estimates (for Belgium, France, Germany, Iceland, Italy, the Netherlands, Spain, Switzerland and the UK) for HZ, PHN and HZO are reported in A0006.

Differences in age ranges, data sources (GPs, Sentinel networks etc), perspective (retrospective, prospective studies), coverage of the population, and time of follow up all make it difficult to compare epidemiological data between countries within Europe.

A gender difference has been reported in several studies, with a higher incidence of HZ in women than in men[15,16,17] while incidence increases with age[15, 16, 18, 19,20,21].

The incidence of HZ is 10–20 times higher in patients infected with human immunodeficiency virus (HIV) than in age-matched HIV-negative participants. HZO incidence ranges from 4%[16], to 10%[22], and as for HZ incidence, it increases with age[15].

The proportion of HZ patients reported to develop PHN varies across studies depending on the PHN definition used and the age of the study population.[33, 23]

Data on HZ mortality are limited but tend to show that fatal cases are likely to be rare especially among immunocompetent, healthy people. HZ is rarely recorded as the cause of death in patients under the age of 65. Age-specific mortality data is only available in the Netherlands; it shows a sharp increase after the age of 80.[24]

Pain is one of the main symptoms of PHN and has both for HZ and PHN a major impact on perceived QoL. Pain and anxiety are the dimensions of the EQ-5D that are most affected by HZ. (A0005)[25,26,27]

In European countries several studies have been conducted to assess health care resource use as a result of HZ and PHN management. The methodologies of these studies differ so direct comparisons are not possible. Hospital records or GP-interviews or databases were the main data sources, and patients could be admitted directly to hospital through the emergency department or referred to the hospital through a specialist doctor or via their GP. The incidences of hospitalisation for HZ or PHN should be integrated with an analysis of the complications presented at admission. That kind of data is reported in few studies, however. Country-specific hospitalisation rates (for Belgium[28], France[15], Germany[16], Italy[33], the Netherlands[17], Spain[32], and the UK[29, 30, 31]) are reported in A0005.

A higher hospitalisation rate is reported for female patients compared with male patients[15, 16, 17]. Average length of stay ranges from 8.1 days[15] to 12.9 days[32].

Few data are available on hospitalisation and PHN. About 2% of PHN cases in Italy result in hospitalisation[33] with quite long lengths of stay (mean stay 10.2 ± 8.6 days). While, in the UK, 11% of hospitalised cases of HZ also had a diagnostic code for PHN [Edmunds 2001]. The case-fatality rate during hospitalisation is high in the over 80 age group, reaching 7.2%[32].

The population eligible for HZ vaccination with Zostavax, those aged 50 years or more, in 2012 in EU-27 countries represented a total of 188 million people (A0023)[34]. It is difficult, however, to assess accurately the number of people in each of the contraindicated groups.

Guidelines recommend the use of oral antiviral agents for the treatment of HZ[35]. Treatment is effective if it is started within 72 hours of the onset of acute symptoms. In a few cases, the therapy is started more than after 72 hours of the onset of acute symptoms because the patient delays the medical visit or because the, often unusual, symptoms of the disease have made diagnosis difficult for the physician. Current treatments for PHN are tricyclic antidepressant drugs (TCAs), alpha-2-delta ligands, opioids and topical agents. Aciclovir, valaciclovir, famciclovir[36] and brivudin have also been used to treat PHN. At the moment, antiviral drugs are not approved for PHN, only for HZ treatment.

Tricyclic antidepressants, gabapentin, pregabalin and 5% lidocaine patches are recommended as first-line treatments for PHN in guidelines issued by the American Academy of Neurology (2004), the International Association for the Study of Pain (2007), and the European Federation of Neurological Societies (2010). Opioids are considered a second-line or third-line therapy in British and Canadian guidelines[37].

Substantial differences in HZ management exist in the different European countries. Many countries lack recent official guidelines for HZ.

Austria refers to German guidelines. German guidelines identify systemic antiviral therapy as first choice[38]. According to one report[39] 58% of incident HZ cases received an antiviral prescription. In The Netherlands prescription of antiviral treatment to HZ patients is relatively uncommon compared with the rates of prescription in the clinical trials on Zostavax. Indeed, one study[40] found that only 22.5% of patients were prescribed antiviral treatment, while in the SPS over 80% of patients received antivirals. The rate of use of antiviral medication among participants with confirmed cases of HZ in the SPS was similar in the two groups (87.3% in the vaccine group and 85.7% in the placebo group).

Zostavax was first authorised in Australia on 02 May 2006. The vaccine was authorised in the EU on 19 May 2006[41, 42, 43] and in the USA on 25 May 2006[2], and the first launch worldwide was in the USA in June 2006. As of December 2012, Zostavax is registered in 54 countries (including the European Union member states).

Two formulations exist and are stored at different temperatures:

- The frozen formulation (stored at minus 15˚C) is approved in seven countries (Australia, the USA, Hong-Kong, Macau, Singapore, Canada and Israel).
- The refrigerated formulation (stored between 4-8˚C) is nowadays the formulation registered in Europe.

The population eligible for HZ vaccination with Zostavax are people aged 50 years or older with the exception of certain groups who have a contraindication[42]. Whereas, in clinical studies, vaccine efficacy was investigated in people aged 60 years or older[3] and aged 50–59 years[1]. Immunocompromised people were excluded both in the SPS[3] and in ZEST[1]. For further details see A0007.

For HIV-infected people the DHHS guidelines[44] and the Advisory Committee on Immunization Practices[45] state that the administration of HZ vaccine is not recommended (See A 0024).

Three studies reported real life data on an HZ vaccination programme conducted in the USA[46, 47, 48]. Vaccine uptake was low (3.9%) especially among older people (over 80 years old). Women were more likely to have undergone vaccination. No data is available on HZ ongoing vaccination programs (A0011). According to a retrospective cohort study of immunocompetent community-dwelling adults aged 60 years or older enrolled in the Kaiser Permanente Southern California health plan, 25% of patients were vaccinated[47]. Individuals in the vaccinated cohort were more likely to be white, to be women, and to have had a larger number of outpatient visits and a lower prevalence of chronic diseases (A0011). Zhang [2012][48] examined the association between HZ vaccination and HZ incidence in selected immune-mediated diseases in a retrospective cohort study conducted among Medicare (USA) beneficiaries (D0017).

The funding/reimbursement of the HZ vaccine is decided at country level and some differences are observed within Europe depending on the healthcare system of the country.

At national level the options are for:

- a programmatic approach with the inclusion of the HZ vaccination in the National Immunisation Programme (NIP), publicly funded and organised after a full assessment performed by a national committee
- the inclusion of HZ vaccine in the reimbursement scheme
- no reimbursement for Zostavax.

Ten countries currently recommend and/or fund HZ vaccination with Zostavax worldwide.

Country	Recommended	Funded/Reimbursed	Age of target population (years)
Austria	Yes	No	50+
Germany	Yes – in Saxony Region	No	50+
Greece	Yes	No	60+
Sweden	No	Yes	50+
UK	Yes	Yes	70-79
Australia	Yes	Process on-going	61-79
Canada	Yes	Process on-going	60+
USA	Yes	Yes	60+
Israel	Yes	No	60+
Korea	Yes	No	60+

Details are reported in A0021.

The main risk factor for HZ and PHN is age, and people aged 50 years or older are much more susceptible than younger people[9].

The use of the HZ vaccine within Europe is decided at country level and some differences are observed according to the healthcare system of the country. Details at country level are reported in A0021.

2.3 Discussion

Attention should be paid to:

- HZ/PHN/HZO incidence and hospitalisation rates at country level. Differences in age ranges, data sources (GPs, Sentinel networks etc), perspective (retrospective, prospective studies), coverage of the population, and time of follow up are all elements that make it difficult to compare epidemiological data at the European level. Further, few data are available on HZ/PHN/HZO mortality.
- The method followed for HZ diagnosis. Criteria followed in the SPS for HZ diagnosis appear to be quite uncommon in real clinical practice. DNA is not always extracted from clinical specimens obtained from participants suspected of having HZ. A wrong diagnosis complicates the interpretation of the results.
- Eligible population. The population aged 50 years or older, in the 27 EU countries amounts to 188 million people. No precise data is available on the numbers of contraindicated groups of patients that are included in that estimate.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY

3.1 Methods

Domain framing

No deviation was required from the general scope of the project when reporting the results in research questions.

Research questions

Element ID	Research question
B0001	What is the technology and the comparator(s)? What is the mechanism of action of the technology?
B0002	What is the approved indication and the claimed benefit of the technology and the comparator?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who performs or administers the technology and the comparator?
B0005	In what context and level of care is the technology used?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator?
B0010	What kind of data and records are needed to monitor the use of the technology and the comparator?
B0011	What kind of registry is needed to monitor the use of the technology and the comparator?

Sources

- Literature from basic search
- Submission file from MAH (SPMSD)
- Summary of Product Characteristics (SPC)
- European Public Assessment Report (EPAR)

The databases used for more specific searches were PubMed, Cochrane, and EMBASE.

Analysis

As most research questions could be answered directly using the SPC and the EPAR, no further formal quantitative or qualitative methods were used to appraise the data.

Synthesis

Most of the research questions could be answered in plain text format.

3.2 Main results

Zostavax® is a lyophilised preparation of live, attenuated vaccine containing VZV (Oka/Merck strain), not less than 19,400 plaque-forming units (PFUs per 0.65 ml dose). Zostavax is manufactured at a higher virus titre (14-fold higher potency) than varicella vaccine. The vaccine is available as a powder and solvent to be made up into a suspension for injection. It is given as a single dose of 0.65 ml injected subcutaneously in the deltoid region of the upper arm. The EMA approved nowadays the refrigerated formulation of Zostavax[41, 42, 43].

One randomised controlled trial (RCT) compared the safety and the immunogenicity of a refrigerator-stable formulation (44,846 PFU/0.65 ml) with those of the frozen formulation (56,845 PFU/0.65 ml) in participants aged 50 years or older[49]. The comparison is intended to show similar antibody titres in the two formulations when measured using glycoprotein enzyme-linked immunosorbent assay (gpELISA). However, this antibody titre is a surrogate marker of threshold for immunity and the use of it has been questioned. The effectiveness of the refrigerated formulation has not been evaluated in a clinical trial covering mortality rates, prevention of HZ and PHN and long-term safety. As a result, follow-up data in daily practice are needed in order to assess whether the refrigerated formulation of the vaccine has an effectiveness and safety profile similar to that of the frozen formulation.

In the SPS the median estimated potency of the HZ vaccine at vaccination was 24,600 PFU and more than 90% of the vaccinated participants received doses lower than 32,300 PFU[3]. The EMA required that one dose (0.65 ml) should contain a minimum of 19,400 PFU.

The detailed information needed to investigate the potential effects of dose potency and duration of protection of the vaccine is not available (B0001)[50].

According to the SPC, Zostavax is indicated for prevention of HZ and HZ-related PHN. It is indicated for immunisation of people aged 50 years or older[3].

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[42].

Contraindications are:

- history of hypersensitivity to the active substance, or to any of the excipients or trace residuals
- 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 people who are receiving topical or inhaled corticosteroids, or low-dose systemic corticosteroids, or in those who are receiving corticosteroids as replacement therapy, e.g., for adrenal insufficiency
- active untreated tuberculosis
- pregnancy; furthermore, pregnancy should be avoided for one month following vaccination[42, 51].

The comparator in the clinical trials is placebo.

Zostavax is administered by a physician or a nurse, so it is utilised in a primary care, outpatient setting. Where a vaccination programme is approved it could be administered in vaccination centres[52].

Linked to Zostavax monitoring data, there are surveillance programmes for HZ. Not all countries have a form of surveillance in place for HZ and, where present, such surveillance shows marked heterogeneity. This surveillance may be bases on already existing national mandatory or sentinel systems and the data collected may only be available in an aggregated form (i.e. for groups of patients with common characteristics).

At national and local levels decisions are taken about the implementation of vaccination programmes for all of the population aged 50 years or older or for specific subgroups. If a vaccination programme is adopted, data should be collected on:

- health status of the target population
- HZ vaccine coverage rates
- HZ vaccine effectiveness
- HZ vaccine adverse events (AEs).

In the USA Zostavax is recommended by ACIP to reduce the risk of shingles and its associated pain in people aged 60 years or older. The vaccine is available in pharmacies and doctor's offices. The choice about whether to get vaccinated is discussed with patients by the doctor[45].

The first-ever national shingles immunisation campaign in Europe has recently been launched in the UK. The vaccination programme will involve people aged 70, with a catch-up programme for those aged up to, and including, 79 years. The programme is planned to start in September 2013[53].

Real and long-term sustainable production capability for Zostavax represented a critical issue in the past. SPMSD declared improvements in the production processes and new manufacturing capacities. Investments have been made by the producer (Merck Sharp & Dohme) in manufacturing, which should allow a better supply of Zostavax worldwide, especially in Europe[54].

3.3 Discussion

According to the SPC, Zostavax is indicated for the prevention of HZ and HZ-related PHN. It is indicated for immunisation of people aged 50 years or older.

Attention should be paid to:

- Differences between the approved formulation (refrigerated and with a minimum vaccine potency of 19,400 PFU) and the formulation of Zostavax studied in the pivotal clinical trials. In pivotal clinical trials the frozen formulation and a potency ranging from 18,700 to 60,000 PFU were studied. Despite the bridging study, the effect of the refrigerated formulation on relevant outcomes, such as prevention of HZ or PHN, has not been studied.
- Contraindicated groups of patients.
- The risk of off-label use in the case of national vaccination programmes or reimbursement schemes. That risk is important given that few cases of HZ/PHN are reported in populations younger than 50 years.
- Monitoring who administers Zostavax; only physicians or nurses should do it.
- Real production capabilities for Zostavax. Real and long-term sustainable production capabilities for Zostavax have represented a critical issue in the past.

4 SAFETY

4.1 Methods

Domain framing

C0001B has been split into 2 subquestions: C0001B1 (most frequently reported side effects) and C0001B2 (severe side effects).

Research questions

Element ID	Research question
C0001A	What kind of harms can use of Zostavax cause to the patient?
C0001B	What are the most frequently reported side effects and what are severe side effects (grade 3 or 4 AE according to Common Terminology Criteria)?
C0004	How will the long term safety be studied/monitored?
C0005	What are the susceptible patient groups that are more likely to be harmed?
C0007	What are the known interactions of Zostavax use?
C0040	What kind of harms are there for public and environment?

Sources

- Literature from basic search. The databases used for more specific searches were PubMed, Cochrane, and EMBASE. Search keys: Mesh terms as indicated in the PICO.
- Submission file from MAH, including update
- SPC of Zostavax
- EPARs of Zostavax
- Risk Management Plan (RMP) of the EMA
- Package insert for Zostavax from the US FDA.

Analysis

In the safety report we focus on the safety profile characterisation of Zostavax compared with placebo. AEs are given by organ system categorised by frequency, seriousness and severity, and reported in a table in accordance with the EMA scheme. A more precise description for AEs is given according to MedDRA Dictionary Terminology.

The frequencies of AEs are designated as:

- Very common ≥ 1/10
- Common ≥ 1/100 to < 1/10
- Uncommon ≥ 1/1000 to <1/100
- Rare ≥ 1/10,000 to < 1/1000
- Very rare < 1/10,000.

Severe side effects are denoted as grade 3 or 4 AE according to Common Terminology Criteria.

Most research questions could be addressed directly using the EMA and FDA documents, so no further formal quantitative or qualitative methods were used to appraise the data.

Synthesis

Most of the research questions could be answered in plain text format. Evidence tables were used in some cases.

4.2 Main results

In the clinical studies, the overall incidence of vaccine-related injection-site adverse reactions was significantly greater for participants vaccinated with Zostavax (frozen formulation) compared with those who received placebo (48% versus 17% in the SPS Substudy and 64% versus 14% in the ZEST)[2]. Vaccine-related systemic adverse effects were more frequent in the vaccinated group (relative risk [RR] 1.29, 95% confidence interval [CI]: 1.05 to 1.57, number needed to treat to harm (NNTH) = 100 SPS population[55], and in the younger participants. The most common side effects with Zostavax are reactions at the site of the injection (redness, pain, swelling, itching, warmth and bruising).

The percentage of participants reporting any systemic clinical adverse experience was greater in the 50 to 59 years age group (ZEST)[1] compared with the 60 years and older age group (SPS)[5]. The safety of Zostavax in immunocompromised individuals has not been established in these studies.

Concomitant administration of Zostavax with influenza vaccine, pneumococcal vaccine or administration of Zostavax in patients treated with systemic corticosteroids (at a daily dose equivalent to 5 to 20 mg prednisone) were generally well tolerated[56, 57].

After HZ vaccination, the risk of serious AEs (SAEs) is (slightly) enhanced compared with placebo treatment in the total cohort of participants aged 60 years and older. The RR is 1.01 (95% CI: 0.85-1.20) for SPS overall (N=37,388; incidence: 1.4% in both study arms) but 1.53 (95% CI: 1.04-2.25) for the Adverse Events Monitoring Substudy (N=6575; incidence: 1.9% in the Zostavax group and 1.3% in the placebo group). In the substudy: there were overall 53% more SAEs (P=0.04) with vaccine than with placebo[2, 58].

The AEs in participants of 50-59 years old was studied in ZEST (N=22,439): The proportion of participants reporting SAEs occurring within the 42-day period immediately after vaccination was similar in the Zostavax (0.6%) and placebo (0.5%) groups (RR 1.13; 95% CI: 0.81–1.60). The corresponding RR value for 182 days immediately after vaccination is an RR of 1.11 (95% CI: 0.92–1.33)[1].

The reported SAEs were: convulsion, gastroenteritis, basal-cell carcinoma, congestive cardiac failure congestive, aortic valve stenosis, arrhythmia, myocardial infarction, acute pulmonary oedema, chronic obstructive pulmonary disease, pneumonia, respiratory failure, upper limb fracture, polymyalgia rheumatica, exacerbation of asthma, anaphylactic reaction and Goodpasture's syndrome[3, 42].

Age is a risk factor for SAEs. In both study arms, the number of participants with one or more severe AEs increases with age. This increase is even greater in the Zostavax group. In the SPS substudy, those aged 80 years or older who had been vaccinated with Zostavax had twice the chance of having an SAE (RR 2.19; 95% CI: 0.75-6.45; P=0.19) after vaccination compared with those given placebo. Participants aged 60 to 69 years old had 21% more risk (P=0.53) and participants aged 70 to 79 years old had 61% more risk (P=0.12) if they were given Zostavax compared with placebo. When the two older groups were combined, there were 75% more SAEs in participants aged 70 and older after vaccination with Zostavax (P=0.03) compared with placebo. The increased risk of SAEs with age after Zostavax vaccination was confirmed by recent safety information provided by the MAH[59].

The most frequently reported AE is vaccine-related reaction at the injection site[2,58].

Within the first 7 days after administration of the vaccine there is a small but significantly increased risk of allergic reactions that require medical attention (RR 2.13; 95% CI: 1.87–2.40 by case-centred method; RR 2.32, 95% CI: 1.85–2.91 by self-controlled case series). Age-related information is not available[60].

Zostavax (frozen formulation) was studied in the subgroup of participants aged 60 years or older until 10 years after vaccination, and in the subgroup aged 50 to 59 years up to

2 years after vaccination. No new clinical studies are planned by the MAH for this specific age group of 50-59 years old. Long-term safety, in addition to the above mentioned follow up, will be monitored by the obligatory updates of the registration authorities (e.g. the Periodic Safety Update Reports and the Vaccine Adverse Event Reporting System). Because the frozen formulation (no longer authorised in Europe) has been replaced in Europe by the refrigerated formulation of Zostavax, data on both formulations should be gathered.

Zostavax is used for prevention, and the intended population is large and healthy. Long-term safety is therefore especially important.

In the SPS overall, no (significant) differences were found to indicate that a specific group of participants is more harmed. There was, however, a trend indicating that the oldest age group, aged 80 years or older, has more SAEs. In contrast to the total study population, the SPS Adverse Events Substudy indicated that SAEs were statistically more frequent in vaccine recipients than in placebo recipients (1.93% vs. 1.29%; risk difference 0.64; 95% CI: 0.04-1.28; P = 0.038)[5]. In those aged 50-59 years old, the proportions of participants reporting SAEs occurring within 42 days after vaccination (Zostavax: 0.6%; placebo: 0.5%) and within 182 days after vaccination (Zostavax: 2.1%; placebo: 1.9%) were similar in the Zostavax and placebo groups[42].

In addition, persons with a contraindication such as a compromised immune status are more likely to be harmed[42].

Zostavax can be administered concomitantly with inactivated influenza vaccine as a separate injection and at a different body site. This is relevant because influenza vaccine is often given to elderly people (mostly 60-65 years old, depending on the country) as an annual vaccination. 23-valent pneumococcal polysaccharide vaccine should not be given together with Zostavax because this concomitant use will reduce the immunogenicity of Zostavax. Concurrent administration of Zostavax and antiviral medications known to be effective against VZV has not been evaluated[42].

Transmission of HZ has not been observed in the clinical trial. 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. It may be that this has not yet been detected because of its low incidence. This is a point for attention in the future[42].

4.3 Discussion

A single dose of Zostavax in immunocompetent participants aged 50 years or older has a low-risk safety profile. The most common side effect observed is a reaction at the injection site.

Concomitant administration of influenza vaccine, pneumococcal vaccines, or administration of Zostavax in patients treated with systemic corticosteroids (at a daily dose equivalent to 5 to 20 mg of prednisone) was generally well tolerated. However, the safety in immunocompromised individuals, such as HIV-infected people, remains to be established. A clinical trial with HIV patients is ongoing.

Compared with placebo, Zostavax vaccination leads to more AEs. As shown in two clinical trials (respectively for participants aged 60 years or older (SPS) and aged 50-59 years or older (ZEST)), the overall incidences of vaccination-related injection-site adverse reactions were 17% and 14% in the placebo groups versus 48% and 64% in the Zostavax groups. The Zostavax group also had more vaccine-related systemic AEs.

Age is a risk factor for SAEs. In both study arms, the number of participants with one or more SAE increases with age. Vaccinees aged 80 years or older are at the highest risk of having an SAE; this age group has more than twice the chance of having an SAE than unvaccinated persons of the same age group. However, it is important to note that the group aged 80 years or older was not a pre-defined age stratum in the SPS. Besides, the (S)AEs with Zostavax were studied using the frozen formulation and not the current refrigerated formulation.

Other items that needed additional information are:

- safety in people with postponed HZ after vaccination (occurrence of HZ in older age)

- the long-term safety of the vaccine
- lack of data on concomitant use of vaccines other than influenza and pneumococcal vaccines
- HZ-like or varicella-like rashes associated with HZ vaccine
- potential risk of transmission of virus by vaccinees to their contacts
- safety profile in immunocompromised people.

5 CLINICAL EFFECTIVENESS

5.1 Methods

Domain framing

D0002B has been split into two sub questions: D0002B1 (Who suffers the most [mortality]?) and D0002B2 (Who suffers the most [pain]?).

Research questions

Element ID	Research question
D0001	What is the expected beneficial effect of vaccination with Zostavax on overall mortality?
D0002A	What is the expected beneficial effect on the disease-specific mortality (due to HZ/PHN)?
D0002B	Who suffers the most?
D0005 D0006	How does Zostavax affect symptoms and findings? How does Zostavax affect progression of disease?
D0011A	What is the relationship between efficacy and age?
D0011B	What is the relationship between efficacy and co-medication/co-vaccination?
D0011C	What is the vaccine efficacy per age group?
D0011D	What are the hospitalisation rates?
D0011E	Is a booster injection needed? If yes, when will that be needed and for whom?
D0016	How does the use of Zostavax affect activities of daily living?
D0012	What is the effect of Zostavax on generic health-related quality of life?
D0013	What is the effect of Zostavax on disease-specific quality of life?
D0017	Was the use of Zostavax worthwhile?

Sources

- Literature from basic search. The databases used for more specific searches were PubMed, Cochrane, and EMBASE. Search keys: mesh terms as indicated in the PICO.
- Submission file of MAH (SPMSD), including update
- SPC of Zostavax
- EPARs of Zostavax
- Package insert for Zostavax from the US FDA.

Analysis

As most research questions could be addressed directly by using the documents from the EMA, the FDA, the pivotal studies and the submission file from SPMSD, no further formal quantitative or qualitative method of appraising the data was used.

Synthesis

Most of the research questions could be answered in plain text format. In addition, evidence tables were used in some instances.

5.2 Main results

The efficacy of Zostavax in reducing the risk of developing HZ has been studied in two pivotal clinical trials: SPS for participants of 60 years and older[3], and ZEST for participants of 50-59 years old (PHN incidence was not assessed in this age group)[1].

Mortality. At the end of the follow-up period of the SPS (mean: 3.13years), 4.1% of all participants (aged 60 years and older) had died[3]. Subgroup analysis showed that the total mortality in participants aged 70 years and older (6.5% or 75/19,270 for Zostavax; 6.2% or 549/10,276 for placebo) was significantly higher than that of those aged 60-69 years (2.1% or 218/19270 for Zostavax and 2.4% or 246/19276 for placebo). A significant difference in the cumulative mortality rates between the age strata 60-69 years versus 70 years and older has been shown (log-rank P<0.001). No specific information was available for participants aged 80 years and older. In the youngest age group in the ZEST (50-59 years)[1], the mortality rate in the vaccine group was low (0% or 1/11,095), while in the placebo group 3/11,116 participants (0%) died.

There is no statistically significant difference in the overall mortality between the Zostavax group (1.03 deaths per 100 person-years) and the placebo group (1.12 deaths per 100 person-years) (stratified log-rank P=0.173; all ages)[1, 5]. Mortality due to HZ is rare, hence any effect on mortality rate would be difficult to detect. Cumulative mortality rates have been calculated by using product-limit estimates for time-to-event data by using a log-rank test stratified by site[5]. The data comparing treatment groups and age strata were: for those aged 60 to 69 years, log-rank P = 0.20; for those aged 70 years or older, log-rank P = 0.37; for the overall treatment comparison: log-rank P = 0.95. The most commonly reported cause of death was cardiovascular disease. Disease-specific mortality was not reported.

In the placebo group, more cases of HZ and PHN have been observed compared with the vaccine group (see ***D0011A*** for Incidences). Although HZ (and to a lesser extent the subsequent condition of PHN) is a potential cause of death, the lower incidence of HZ in the vaccine group did not result in a lower number of deaths. The overall mortality rates were similar in the Zostavax and placebo groups.

The rates of HZ-related hospitalisation in the vaccine group and the placebo group did not show a statistically significant difference.

Conclusion mortality: Over the entire course of the study, the rates of death in the total SPS population were higher in the older age stratum (aged 70 years or older: 6.5% for

Zostavax and 6.2% for placebo) than in the younger age stratum (aged 60-69 years: 2.1% for Zostavax and 2.4% for placebo). This reflects the differences in mortality between the age groups in the general population. The mortality rates were similar in the two treatment groups both in the total population and in the age groups. Zostavax vaccine has not been demonstrated to affect overall mortality. Moreover, no data were available on the effect of Zostavax on disease-specific mortality. These results may be related to the very low number of HZ-related deaths; effects of the vaccination on HZ-related mortality may be difficult to detect, especially in patients younger than 80 years. Therefore, any influence of HZ-related mortality on total mortality will be negligible.

Incidence. In a time-to-event analysis, the cumulative incidences of HZ and of PHN were both significantly lower in the vaccine group compared with the placebo group (P<0.001).

The *incidence of HZ* (per 1000 persons-years) increased with age both in the vaccine group (1.8 at ages 50-59 years; 3.9 at 60-69 years; 6.7 at 70-79 years; and 9.9 at 80 years and older) and in the placebo group (6.67 at ages 50-59 years; 10.8 at 60-69 years; 11.4 at 70-79 years; and 12.2 at 80 years and older) although the incidences in the intervention group were lower. In the modified intention-to-treat population, Zostavax significantly reduced the risk of developing HZ when compared with placebo[1, 3]. The vaccine efficacy for the prevention of HZ was the highest for participants aged 50-59 years and the vaccine became less effective with increasing age of those vaccinated (72% at ages 50-59 years, 64% at 60-69 years, 41% at 70-79 years and 18% at 80 years and older). According to a Cochrane review[55], the number needed to treat to benefit (NNTB) is 50. However, this is an estimate for the overall group. Information about age specificity is not available.

The *incidence of PHN* increased with age, both in the vaccine group and in the placebo group. The incidences per 1000 person years were, in the vaccine group, 0.26 for 60-69 years old and 0.71 for those aged 70 years and older, and in the placebo group the corresponding incidences were 0.74 and 2.13. The vaccine efficacy of Zostavax in reducing the risk of PHN can be expressed either for the total study population or for participants who develop HZ after vaccination. In the SPS, there were 107 cases of PHN, 27 in the vaccine group and 80 in the placebo group (0.46 versus 1.38 cases per 1000 person-years, respectively; P<0.001). Overall, the vaccine efficacy (percentage reduction compared with the placebo group) for PHN was 66.5% (95% CI: 47.5 to 79.2; P<0.001) of the total population. There were no significant differences in the vaccine efficacy for PHN when the results were stratified according to age. Vaccine efficacy for PHN was not investigated in the 50-59 year age group[1, 3].

Among participants who develop HZ after vaccination, the vaccine efficacy for PHN is lower than in the total population. The VE is in that case 39% (95% CI: 7 to 59%) overall; 5% (95% CI: -107 to 56%) for ages 60-69 years; 55% (95% CI: 18 to 76%) for ages 70-79 years and 26% (-95% CI; -69 to 68%) for ages 80 years and older. Thus, for the specific prevention of PHN, Zostavax is most active in people aged 70-79 years, somewhat active in those aged 80 years and older, and almost inactive in the 60-69 years age group[3]. The Cochrane review[4], using a different, more strict definition of PHN as persistent or recurring pain more than 120 days instead of 90 days after initial development of the rash, in contrast concluded that there was no evidence that Zostavax reduced the incidence of PHN beyond its effect on the incidence of HZ in the total group of patients aged 60 years and older. However, there may be an effect on the prevention of PHN by Zostavax in certain age groups (e.g. 70-79 years). More data are required to demonstrate this conclusively.

Burden. According to Oxman (2005)[3], HZ vaccine shortens the duration of the pain (as measured with the use of Zoster Brief Pain Inventory) by 3 days (21 days versus 24 days, P=0.03). However, according to the FDA and the EMA, this effect is even smaller (2 days, *i.e.* 20 days versus 22 days). Because specific data about the severity of the pain is not available, the clinical relevance of a reduction of 2 to 3 days is not clear. Moreover, a reduction of less severe pain (pain score <3) was observed only in the younger age group (30 versus 36 days), while for the group of older participants no difference was

found compared with the placebo group (pain score <3, median duration 41 days for both groups).

The use of the Zostavax reduced the burden of illness (*BOI*) due to HZ in an age-dependent manner. BOI is a composite endpoint affected by the incidence, severity and duration of the associated pain and discomfort due to HZ. The vaccine efficacy for the BOI decreases with age from 73.0% for ages 50-59 years[1], to 65.5% for ages 60-69 years, to 59% for ages 70-79 years and 38% for ages 80 years and older[7]. BOI is a composite endpoint; therefore it is unclear whether the reduction resulted from reductions in the incidence, the duration, or the intensity of the pain or by a combination of these parameters. The vaccine efficacy for the BOI is calculated by a complex method to summarise the effect of HZ over time. To capture the degree and duration of the effect of HZ, a ''burden of interference'' score is calculated from the area under the curve created when the effect of HZ is plotted against time. In essence, time is used as a multiplier of the effect of HZ on pain. A problem with this method is that small differences in HZ pain-related measures over a long period of time can have a large effect on the score but may not be clinically meaningful. This would lead to an overestimation of vaccine effectiveness.

Conclusion incidences and burden: The vaccine efficacy of Zostavax on the incidence of HZ is on average over 50%. This effect is age dependent. The higher the age, the lower the effect. An effect of Zostavax on preventing PHN or a clinically relevant reduction of the pain has not been shown. The effect of Zostavax on the BOI is predominantly attributable to its effect on the incidence of HZ.

According to the EMA, Zostavax can be administered concomitantly with inactivated influenza vaccine as separate injections and at different body sites. This is relevant because influenza vaccine is often given to elderly people (mostly 60-65 years old) as an annual vaccination. 23-valent pneumococcal polysaccharide vaccine should not be given together with Zostavax because concomitant use will reduce the immunogenicity of Zostavax.

According to the SPC, people with a history of HZ and VZV-seronegative or low seropositive people are not contraindicated. Zostavax is also not contraindicated for use in people who are receiving topical or inhaled corticosteroids or low-dose systemic corticosteroids or in those receiving corticosteroids as replacement therapy, e.g. for adrenal insufficiency. Immunosuppressive therapy (including high-dose corticosteroids), and primary and acquired immunodeficiency states are designated as contraindications. The efficacy of Zostavax has not been established in adults with HIV/AIDS; the use of Zostavax in this case is also contraindicated.

The rates of HZ-related hospitalisation in the Zostavax group and the placebo group did not show a statistically significant difference in the SPS and ZEST. In the clinical trials, older age is associated with a higher cumulative hospitalisation rate irrespective of the treatment. Although vaccination with Zostavax reduces the incidence of HZ, this vaccine has no beneficial effect on hospitalisation due to HZ.

Vaccine efficacy persists for at least 7 years. A study of the long-term persistence of efficacy, for up to 10 years after vaccination, was conducted as part of the pharmacovigilance activities required by the EMA. It is not known whether a booster is needed and if so, when. There is also a lack of knowledge about the effectiveness and safety of a second dose of the vaccine.

Different conclusions were reached in different reports about the efficacy of the HZ vaccine on HZ-related interference with ADLs and health-related quality of life (HRQL), even though both publications of Schmader (2010)[61] and Gagliardi (2012)[55] analysed data from the SPS population. According to Schmader (2010), for the modified intention-to-treat population, the overall HZ vaccine efficacy was 66% (95% CI 55–74%) for the ZBPI ADL burden of interference score and 55% (95% CI 48–61%) for both the SF-12 mental component summary (MCS) and physical component summary (PCS) scores. Of participants who developed HZ, HZ vaccine reduced the ZBPI ADL burden of interference score by 31% (95% CI: 12–51%) and did not significantly reduce the effect on HRQL. The

authors of Schmader (2010)[61] concluded that Zostavax reduced the effect of HZ on HRQL in the overall population of vaccinees but not in vaccinees who developed HZ.

According to Gagliardi (2012), who only analysed the more severe cases of ADL interference (severity of interference score of 300 or greater), there were no significant differences between vaccinated and placebo groups for ZBPI ADL, in the SPS population (RR 0.63, 95% CI: 0.34 to 1.16). According to Gagliardi the impact of vaccination on quality of life was poorly reported[55]. Based on the SPS data, it was concluded that the vaccine reduced the number of participants with severe quality of life impairment caused by acute pain from herpes zoster.

Recalculation of the interference of ADL for this assessment is not feasible because the input data needed are not available and the computation of the ZBPI scores is extremely complex. Data on disease-specific quality of life were not available.

RCT results on the ability of Zostavax to prevent HZ have been confirmed in the real life studies. However, the vaccine efficacy seems to be lower than in the setting of a clinical trial (D0017).

In the study of Tseng (2011)[47] vaccination was associated with a reduced risk of herpes zoster (hazard ratio [HR] 0.45; 95% CI: 0.42-0.48), with a vaccine efficacy for incidence of HZ of 0.55. While in Zhang (2012)[48] vaccine efficacy for incidence of HZ is in this case 0.39 (95% CI 0.39-0.48).

In the study of Langan (2013)[46], the overall vaccine efficacy for herpes zoster in vaccinees was 0.48 (95% CI 0.39–0.56), in the subgroup of immunosuppressed individuals, vaccine efficacy against zoster was 0.37 (95% CI: 0.06-0.58). The incidence rates for herpes zoster were higher in older age groups, in women, and in immunocompromised persons[46].

Vaccine efficacy for incidence of PHN was reported in the study of Langan 2013[46]. After adjusting for patient characteristics and comorbidities the vaccine efficacy for incidence of PHN was calculated as 0.59 (95% CI: 0.21-0.79)[46].

5.3 Discussion

With increasing age, the incidence of HZ, the incidence of PHN, the BOI, hospitalisation and ultimately the mortality due to HZ all increase. As a result elderly people are most affected by HZ and are the most appropriate target population for HZ vaccine.

In SPS and ZEST, data on vaccine efficacy (for preventing HZ, preventing PHN, lowering mortality and reducing the BOI) were reported for different age groups.

Zostavax does not decrease overall mortality and there is no evidence that it affects disease-specific mortality. Furthermore, there is no evidence that HZ vaccine reduces hospitalisation rates.

Zostavax was effective in reducing the incidence of HZ by 51% on average. The vaccine efficacy for HZ incidence decreases with increasing age from 72% at age 50-59 years to 64% at 60-69 years, to 41% at 70-79 years and to only 18% at 80 years and over.

The vaccine efficacy for preventing PHN is 67% on average when compared with placebo for the total study population, and this effect is consistent through the different age strata. However, the condition of PHN can exist only in those who develop HZ, either in the placebo arm or as a breakthrough despite HZ vaccination. If vaccine efficacy is calculated for the participants who develop HZ after vaccination, the beneficial effect of Zostavax is less substantial and shows more variability through the age groups. The vaccine efficacy for preventing PHN is, in this case, 39% on average, 5% for ages 60-69 years, 55% for ages 70-79 years and 26% for ages 80 years and older. The efficacy of Zostavax in preventing PHN beyond its effect on the incidence of HZ remains uncertain. It is important to realise that the vaccine efficacy for PHN depends on the definition of PHN.

No significant evidence emerged in favour of HZ vaccination when the definition of PHN used was pain persisting or recurring more than 120 days after the onset of HZ [Chen 2011].

The effect of HZ on HRQL and BOI in vaccinees who developed HZ after vaccination is not clear. After vaccination, the vaccine efficacy for the BOI seems to decrease with increasing age. Younger participants seemed to benefit more than older ones. However, the vaccine efficacy for the BOI is a composite endpoint calculated by multiplying diverse parameters. The main purpose of composite endpoints is improve the statistical efficiency of a trial [EUnetHTA guideline on Composite endpoints, 2013], because they facilitate higher event rates. The results can be influenced by one of the components in relation to the other [EUnetHTA guideline on Composite endpoints, 2013]. The major limitation of composite endpoints, like the vaccine efficacy for the BOI, is that they can be difficult to interpret and their incorrect interpretation may result in overestimation of the effects of an intervention. In this case, it seems that the effect of the vaccine on the incidence of HZ has by far the largest impact on the measured effect on BOI. But it is also possible that the calculated effect results from multiplying artifacts. If the composite endpoint is reduced to its component endpoints, no significant effects of Zostavax can be shown apart from the effect on the incidence of HZ.

The results for the influence of Zostavax on ADL were inconclusive. Again, this is a composite outcome obtained by calculation and multiplication. The methodology used was highly complicated and not validated for the target population of this assessment. Based on the same dataset, two authors came to opposite conclusions. The usefulness of these data is therefore limited.

Information about the exact duration of the effect after vaccination is also needed to estimate whether a booster will be needed and if so, when.

The study results have some major limitations, the most important of which are:

- Despite the high number of participants, the sample size may still be too low to detect a possible effect of the vaccine on the incidence of PHN in patients with HZ.
- After initial registration, the formulation of Zostavax has been changed from a frozen one to a refrigerated one. Although the bridging study showed comparable VZV antibody geometric mean titres in the two formulations, the effect of the refrigerated formulation on relevant outcomes, such as prevention of HZ or PHN, has not been studied.
- People with compromised immunity were excluded from the studies (contraindication). There is no information about the effectiveness of Zostavax in this group that may need HZ prevention the most.
- People who have been vaccinated can became immunocompromised later, through senescence, disease or medication. It is not clear whether these people will be more susceptible to the reactivation of VZV.
- The primary endpoint in the studies (vaccine efficacy for BOI) is a composite endpoint. Such endpoints can be difficult to interpret and their incorrect interpretation may lead to overestimation of the effects of an intervention. It is also possible that the calculated effect results from multiplying artifacts. Analysis of the individual parameters separately partly covers this problem.
- Pain control and quality of life are key factors for the affected patient. The method of pain assessment used in the clinical trials is open to question. Besides the methodological limitations of the study Schmader (2010)[61], there are doubts about the clinical relevance of the measured scores to denote the severity of the pain.
- The oldest age group is most vulnerable, but the oldest elderly (participants aged 80 years and older) was not a prespecified subgroup in the studies. The posthoc analysis of this relatively small subgroup entails uncertainties.
- Long-term data on safety and efficacy after 10 years is lacking. Therefore, the relevance of an eventual revaccination cannot be assessed within the remit of this report.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE THAT WAS USED

Methods

Project approach and method

The following sources of information were used:

- The submission file of Sanofi Pasteur MSD received on April 12th 2013.
- The summary of product characteristics (SmPC) and public assessment reports (EPAR) of the registration dossier by EMA, including the underlying clinical studies published in peer reviewed journals.
- Official assessment reports or (inter)national recommendations concerning zoster vaccine.
- A non-systematic literature search in the databases of Medline, Embase and Cochrane using the mesh terms as described in the project scope (PICO). This in addition to the literature search as carried out by the applicant. *

Quality assessment tools or criteria that were used:

- The internal validity and external validity of the studies was assessed according to the EUnetHTA guidelines#.

Methods for synthesis that were used [such as]: evidence table, plan for meta-analysis or qualitative synthesis, use of GRADE, etc.

- evidence tables presenting data, if possible per age group.
- meta analysis for the age groups: *not assessed. It was not feasible because of lacking information; not all relevant age groups were pre-specified strata. Instead of a meta analysis (and in case that data were available), a trend analysis was performed to estimate the age dependency of the outcome parameters.*

* A complete systemic literature review during the assessment period of the REA was not feasible in due time. Therefore the literature search carried out by Sanofi Pasteur MSD on 21/03/2013 was repeated on 07/06/2013. No relevant clinical trials were missing.

#EUnetHTA guideline. Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals. 2013. Available at: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Applicability.pdf

EUnetHTA guideline. Internal validity of randomized controlled trials. 2013. Available at http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Internal_Validity.pdf

Preliminary evidence table
Author, year, reference number/journal
Country of the trial
Sponsor
Comparator
Study design
Number of the studied population, if possible specified to age groups according to PICO
Patient characteristics in both arms, if possible specified to age groups according to PICO
Duration follow-up, if possible specified to age groups according to PICO
Potential risk of bias
Dropouts/lost for follow-up, if possible specified to age groups according to PICO
Outcomes (specified to age groups according to PICO if possible)
Efficacy
- incidence of HZ
- incidence of PHN
- overall survival (mortality)
- progression free survival (recurrence)
- burden of illness
- severity of the pain
- duration of the pain
- hospitalisation
- quality of life
- ADLI (daily life)
Safety
- most frequently reported side effects
- serious side effects (CTCAE grade 3 or 4).
- numbers of persons with one or more frequently side effects
- numbers of persons with one or more serious side effects
- mortality

Description of the evidence that was used

Table 1. Characteristics of the randomized controlled studies of Zostavax as compared with placebo.

Study	Time	Study type	N	Intervention (N)	Comparator (N)	Patient population	Endpoints	Duplicate publications from the same study
Zostavax (Oka/Merck VZV vaccine, zoster vaccine, frozen formulation; a single dose of 0.65 ml containing not less than 19400 PFU, subcutaneously administered) versus placebo								
I. Shingles Prevention Study (SPS). In- and exclusion criteria/sponsors: see [A].	1998-2004. Enrolment: from 11/1998 to 09/2001. Follow-up through 04/2004 (mean 3.13 years; range 1 day to 4.90 years).[1]	Randomised, placebo-controlled, double-blind at 22 sites in the United States. This study performed 2 ITT analyses, with all individuals developing HZ (ITT) and only with those who developed after 30 days from the vaccine injection (modified ITT). For the REA we considered the modified ITT.	38,546	19,270	19,276	Immunocompetent adults ≥ **60 years** old, with history of varicella or had resided in the continental US for at least 30 years. Median age in both groups was 69 years, ~ 59% male and 95.4% white race.	1st: Burden of illness due to herpes zoster, a measure affected by the incidence, severity, and duration of the associated pain and discomfort. 2nd: incidence of post herpetic neuralgia. Outcomes: see note.[2]	[Oxman 2005] Also using the SPS population: [Schmader/ Oxman 2012 (218)] and [Schmader/ Johnson 2010 (215)]
Zostavax (Oka/Merck VZV vaccine, zoster vaccine, frozen formulation; a single dose of 0.65 ml containing not less than 19400 PFU, subcutaneously administered) versus placebo								

[1] Pain and discomfort associated with herpes zoster were measured repeatedly for six months. AE occurring within six weeks were recorded.
[2] Confirmed cases of HZ, cases of HZ within 30 days of vaccination, confirmed HZ cases and all adverse events occurring within 42 days after vaccination and during the whole study. Participants with follow-up, participants with one or more AEs (systemic or injection site), participants with serious AEs, vaccine-related AEs (systemic or injection site), death, varicella-like rash at injection site and not at injection site, herpes zoster-like rash, rash unrelated to HZ, participants hospitalised, hospitalisation related to HZ, AE by age 60 to 69 years old and ≥ 70 years old.

Study	Time	Study type	N	Intervention (N)	Comparator (N)	Patient population	Endpoints	Duplicate publications from the same study
II. Adverse Event Substudy of the SPS. Prompts for reporting AE: [B]. In- and exclusion criteria/sponsors: see [B].	See under SPS.	See under SPS.[3] Participants in the substudy were <u>not</u> randomly selected.	6,616	3,345	3,271	See SPS	Adverse events.	[Simberkoff and Arbeit 2010 (208)]
Zostavax (Oka/Merck VZV vaccine, zoster vaccine, frozen formulation; a single dose of 0.65 ml containing not less than 19400 PFU, subcutaneously administered) versus placebo								
III. Zoster Efficacy and Safety Trial (ZEST). Participants characteristics:[C]. In- and exclusion criteria/sponsor: see [D].	10/2007 to 01/2010. Mean follow-up: 1.3 years	Randomized, placebo-controlled, double-blind study of 105 sites in North America and Europe.	22,439	11,211	11,228	Healthy participants aged **50–59 years** with a history of varicella or residence in a VZV-endemic area childhood disease) for ≥.30 years. Mean age in both groups was 55 years, 38 % male and 94.4% white race.	<u>Efficacy</u> 1st:incidence of herpes zoster. 2nd: severity-by-duration score of HZ acute pain; <u>Safety</u> 1st: incidence of serious adverse event.	[Schmader and Levin 2012 (207)]

[3] Approximately 300 subjects per site were enrolled in an Adverse Events (AE) Substudy. During the 42 days after vaccination, these subjects maintained a daily log of body temperature and a Vaccination Report Card of clinical symptoms and injection site complaints. During the remainder of the study, they were actively followed by the ATRS (Automated Telephone Response System) and site personnel to identify all hospitalisations.

Table 2. Relevant non-RCTs identified

Trial no./ Primary reference source	Study design	Objective	Intervention(s)	N	Patient population	Endpoints	Justification for inclusion
Gagliardi 2012	Cochrane review	To evaluate the effectiveness and safety of vaccination for preventing herpes zoster in older adults.	We included clinical trials that compared herpes zoster vaccine, of any dose and potency,with at least one of the following comparison groups. 1. Any other type of intervention (for example, varicella vaccine, antiviral medication). 2. Placebo. 3. Nothing (no vaccine).	52,269	Older adults (mean age ≥ 60 years). Participants with immunosuppressive disorders were excluded.	**Primary outcomes:** 1. Incidence of herpes zoster, diagnosed according to the criteria (clinical and/or laboratory) established by the primary studies. **Secondary outcomes** 1. Adverse events: local or systemic reactions (for example, pain, pruritus, swelling, headache) occurring at any time after vaccination. 2. Mean duration of vaccine protection.	Systematic review including SPS.
Chen 2011	Cochrane review	To assess the efficacy and safety of vaccination in preventing postherpetic neuralgia.	1. VZV vaccination versus no vaccination. 2. VZV vaccination versus placebo. 3. VZV vaccination versus other interventions. We excluded studies comparing different potencies of vaccine. We excluded studies without a valid control group, as the effect of the vaccine could not be assessed.	38,546	Any person who was administered the herpes zoster vaccine and control participants.	**Primary outcomes:** The incidence of PHN at least four months after the onset of the acute herpetic rash. We defined PHN as pain associated with herpes zoster, persisting or recurring at the site of shingles more than 120 days (**four months**) after the onset of herpes zoster rash. **Secondary outcomes:** 1. Pain severity measured by a validated scale, such as the 0 to 10 numerical rating scale (0 = no pain, 10 = worst possible pain) after four or six months (Cruccu 2004). 2. Adverse events within six weeks after vaccination. Adverse events were categorised as serious and non-	Critical review of SPS

Trial no./ Primary reference source	Study design	Objective	Intervention(s)	N	Patient population	Endpoints	Justification for inclusion
						serious. We defined serious events as those that are life-threatening, which require or prolong hospitalisation, cause death or result in persistent or significant disability. All other adverse events were considered non-serious.	
Fried 2010	Comment on SPS.	See SPS	See SPS	See SPS	See SPS	See SPS	Adding P-value SAE for age strata

Table 3. List of ongoing studies with Zostavax

Study	Time	Study type	N	Intervention	Comparator	Patient population	Endpoints
NCT01262300 Vitamin D supplementation and varicella zoster virus vaccine responsiveness in older long-term care residents.	Recruiting November 2010-August 2014 (Final data collection date for primary outcome measure).	Phase 1	150	Zostavax	None	Aged ≥ 60 years. Residing in a long-term care facility. Have not yet received VZV vaccine.	VZV-specific cell mediated immunity, as measured by the interferon-γ ELISPOT assay. VZV-gpELISA to measure the VZV-specific antibody concentration. VZV-specific effector and memory T cells.

Study	Time	Study type	N	Intervention	Comparator	Patient population	Endpoints
NCT01137669 Phase I trial, ZOSTAVAX® prior to renal transplantation	Recruiting September 2010-April 2013 (Final data collection date for primary outcome measure).	Phase 1	40	Zostavax	Placebo	Age 18 years or older at the time of vaccination. Chronic kidney disease (CKD) activated on the United Network for Organ Sharing (UNOS) deceased donor waitlist or anticipating living donor renal transplant no sooner than 4 weeks following vaccination. Varicella Zoster Virus (VZV) seropositive by local laboratory or Center for Disease Control (CDC) serologic testing. Negative pregnancy test.	Safety: incidence of grade 3 or higher vaccine related adverse events (AEs) and vaccine related serious adverse events (SAEs). Biopsy proven graft rejection. Safety: incidence of vaccine related serious adverse events (SAEs). Safety: increase of panel reactive antibody (PRA) by greater than or equal to 10% (e.g., from 10% to 20%) or newly positive donor specific cross match (DXM) after immunization and prior to transplantation in the absence of any other attributable cause. Safety: any occurrence of proven [polymerase chain reaction (PCR) confirmed] vaccine strain varicella zoster virus (VZV) infection at any site not contiguous with the injection site.
NCT01600079 Post-licensure observational study of the long-term effectiveness of ZOSTAVAX™	Recruiting May 2012-October 2023 (Final data collection date for primary outcome measure)	Observational	30000	Zostavax	None	Member of Kaiser Permanente Northern California (KPNC). ≥ 50 years of age.	Incidence of Herpes Zoster in Vaccinated and Unvaccinated Cohorts, Overall, and by Age (50-59, 60-69, ≥70) at Vaccination [Time Frame: 10 years] Incidence of Severe Herpes Zoster Including Postherpetic Neuralgia in Vaccinated and Unvaccinated Cohorts, Overall, and by Age.
NCT00940940 Safety and immunogenicity of Zostavax vaccine in patients undergoing living donor kidney transplantation	Recruiting (at last update) October 2009-June 2013 (Final data collection date for primary outcome measure).	Phase 4	40	Zostavax	Placebo	18 to 65 years. Listed or will likely be listed for live donor kidney transplant within one month.	Immunogenicity [Time Frame: 6 months]

Study	Time	Study type	N	Intervention	Comparator	Patient population	Endpoints
NCT01573182 A phase II clinical trial of vaccination of stem cell donors with Zostavax to reduce the incidence of herpes zoster in transplant recipients - A pilot study.	ongoing, but not recruiting participants April 2012-December 2014 (Final data collection date for primary outcome measure).	Phase 2	40	Zostavax	None	Allogeneic HSCT recipient-donor pair, donor aged 50 years and over.	Percentage of transplant recipients with VZV specific T cell proliferation within the first 12 moths post-tranplant. Donor VZV positivity by PCR and genotype and donor VZV specific T cell response to vaccination
NCT01288014 Relationship of cytokine production and immune responses to Varicella Zoster Virus (VZV) in elderly recipients of zoster vaccine.	Recruiting (at last update) January 2011-March 2012 (Final data collection date for primary outcome measure).	Observational	26	Zostavax	None	60 to 80 years.	Development of antibodies, cellular immunity, and cytokines before and after vaccination [Time Frame: Up to week 6]
NCT01474720 Immunologic response to varicella zoster vaccination with Zostavax in patients with systemic Lupus Erythematosus.	Recruting (at last update) November 2011-July 2012 (Final data collection date for primary outcome measure).	Phase 1	20	Zostavax	None	Age ≥ 50 years. History of primary varicella vaccination or positive VZV IgG antibodies. Diagnosis of SLE according to ACR criteria for > 1 year.	Cell-mediated immune response to varicella at 12 weeks following vaccination Antibody response to Zostavax vaccination Adverse events

Study	Time	Study type	N	Intervention	Comparator	Patient population	Endpoints
NCT01506661 Immune response to varicella zoster vaccination (ZOSTAVAX) in subjects with rheumatoid arthritis.	Recruiting (at last update) January 2012-July 2012 (Final data collection date for primary outcome measure).	Phase 1	20	Zostavax	None	50 to 80 years. History of primary varicella vaccination or positive VZV IgG antibodies. Diagnosis of RA according to ACR criteria for > 1 year, or healthy (control) participants. Stable, mild disease activity as defined by a DAS28 score of 4.0. Current medical treatment for RA has been stable for 4 weeks prior to screening. Acceptable immunosuppressive medications.	Safety: adverse events Immunogenicity
NCT01331161 Systems biology of zoster vaccine (ZOSTAVAX®) in young and elderly	Ongoing (at last update) July 2011 - April 2012 (Final data collection date for primary outcome measure).	Interven tional	77	Zostavax	None	Immunocompetent participants aged 25-40 years, or community dwelling participants between the ages of 60-79.	Number of participants with innate immunity signatures that correlate with the T cell adaptive immunity responses after ZOSTAVAX. The number of participants with innate immune signatures that correlate with the B and T cells adaptive immunity responses after ZOSTAVAX.
NCT01245751 Safety, tolerability and immunogenicity of a booster dose of ZOSTAVAX™ administered ≥10 years after a first dose compared with a first dose of ZOSTAVAX™.	Active, not recruiting (at last update) April 2011- July 2012 (Final data collection date for primary outcome measure).	Phase 3	600	Zostavax Group 1: Booster Dose	Zostavax Group 2: First Dose Participants ≥70 years of age. Group 3: First Dose Participants ≥60 and <70 years of age.	50 years and older. Must not have a fever of ≥100.4˚ F on the day of vaccination. Any underlying chronic illness must be in stable condition.	Geometric mean titer (GMT) of the antibody responses to Varicella Zoster Virus (VZV). Geometric mean fold rise (GMFR) in VZV antibody titers. Number of participants reporting one or more adverse experiences.

Study	Time	Study type	N	Intervention	Comparator	Patient population	Endpoints
					Group 4: First Dose Participants ≥50 and <60 years of age.	History of Varicella or residence in a VZV-endemic area for ≥30 years.	
NCT01391546 An open-label, randomised, comparative, multicentre study of the immunogenicity and safety of ZOSTAVAX when administered by intramuscular route or subcutaneous route to subjects of 50 years of age and older.	Active, not recruiting (at last update) June 2011 - June 2013 (Final data collection date for primary outcome measure)	Phase 3	354	ZOSTAVAX intramuscular (IM) route	ZOSTAVAX subcutaneous (SC) route	50 years and older. Varicella history-positive or residence for >30 years in a country with endemic VZV infection.	VZV glycoprotein enzyme-linked immunosorbent assay (gpELISA) antibody Geometric Mean of Titres (GMT). VZV gpELISA antibody Geometric Mean Fold Rise (GMFR) in the intramuscular arm.
NCT00851786 A phase II, randomized, double-blind, placebo-controlled clinical trrial to evaluate the safety, tolerability, and immunogenicity of ZOSTAVAX® (zoster vaccine live) in human immunodeficiency virus (HIV)-1-Infected adults on potent combination ART with conserved immune function	This study has been completed.	Phase 2	395	ZOSTAVAX	Placebo	18 years and older. HIV infected. Use of potent combination ART regimen within 90 days prior to entry and undetectable plasma HIV RNA level within 90-210 days prior to study entry. CD4 cell count of at least 200 cells/microL obtained within 30 days prior to study entry. Laboratory values obtained within 90 days prior to study entry: Hemoglobin 7.0 g/dL or	Number of participants With composite safety endpoint of the occurrence of serious adverse events (SAEs) or division of AIDS (DAIDS) Grade 3 and 4 signs and symptoms, excluding SAEs related to trauma.

Study	Time	Study type	N	Intervention	Comparator	Patient population	Endpoints
						greater; Platelet count 50,000/mm3 or greater; Creatinine 3 x ULN or less; AST (SGOT), ALT (SGPT), and alkaline phosphatase 5 x ULN or less.For females of reproductive potential, a negative serum or urine pregnancy test within 24 hours prior to study entry. Willing to use accepted forms of contraception for the duration of the study. History of varicella or herpes zoster more than 1 year prior to vaccination or VZV seropositivity at any time prior to entry.	

Ad table 1-I.

A: Shingles Prevention Study, in- and exclusion criteria.

Inclusion Criteria:

a) History of varicella or long term (at least 30 years) residence in the continental USA
b) 60 years of age or older
c) Informed consent was obtained from the subject.

Exclusion criteria:

a) Immunosuppression resulting from disease (e.g., malignancy, HIV infection), corticosteroids (except intermittent topical or inhaled corticosteroid [<800 mcg/day beclomethasone dipropionate or equivalent]), or other immunosuppressive/cytotoxic therapy (cancer chemotherapy or organ transplantation);
b) Active neoplastic disease (except local skin cancer or other malignancies [e.g., prostate cancer] that are stable in the absence of immunosuppressive/cytotoxic therapy);
c) Prior herpes zoster;
d) Prior receipt of varicella vaccine;
e) Allergic sensitivity to neomycin or;
f) History of anaphylactoid reaction to gelatin;
g) Significant underlying illness that would be expected to prevent completion of the study (e.g., life-threatening disease likely to limit survival to less than 5 years).
h) Subject was not ambulatory (bed-ridden or homebound);
i) Receipt of immune globulin or any other blood product within 3 months before or planned during the 3-5 year study period;
j) Receipt of any other immunizations within one month before study vaccination (2 weeks in the case of inactivated influenza vaccines or other non-replicating immunization products [e.g., dT, pneumococcal vaccine, hepatitis A caccine, hepatitis B vaccine]), or scheduled within 6 weeks after study vaccination.
k) Subject was currently receiving antiviral therapy;
l) Any other condition (e.g., extensive psoriasis, chronic pain syndrome, cognitive impairment, severe hearing loss) that, in the opinion of the investigator, might interfere with the evaluations required by the study;
m) Subject had an intercurrent illness (e.g., urinary tract infection, influenza) that might interfere with the interpretation of the study;
n) Subject was female and pre-menopausal (women who enter the study must be post-menopausal);
o) Subject was unlikely to adhere to protocol follow-up;
p) Subject was involved in a conflicting (vaccine or investigational drug) clinical trial.

Sponsors and collaborators:

- Department of Veteran Affairs
- Merck
- National Institute of Allergy and infectious Diseases (NIAID)*

*__Source:__ *Adapted from 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(22):2271-84.*

Ad table 1-II.
B: Adverse Events Substudy of the SPS: prompts for reporting adverse events within the 42 day safety follow-up period.

Questions asked of participants on day 43 or later regarding adverse events occurring within the first 42 days after vaccination:

1. Since the day of vaccination have you had a rash that has not been seen by us?
2. Since the day of vaccination have you had any unusual reactions that you have not reported to us?
3. Since the day of vaccination have you been hospitalized for any reason?
4. Since the day of vaccination have you experienced anything that resulted in a disability?
5. Since the day of vaccination have you experienced anything that was life threatening?
6. Since the day of vaccination have you been diagnosed with cancer?
7. Since the day of vaccination have you had an overdose of any medication?

These questions were included in the automated telephone response system call on day 43 and in a questionnaire that was inserted into the vaccination report card. An answer of "Yes" to any of these questions led to follow-up by a study coordinator to collect more information on the adverse event. Confirmed responses to questions 3–7 led to a serious adverse event (SAE) report.

The participants maintained a daily log of body temperature and a "report card" of symptoms related to the injection site and other clinical symptoms during the 42 days after vaccination. Thereafter, they were followed to identify all hospitalisations.

*__Source:__ *Adapted from 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(22):2271-84.*

Ad table 1-III.
C: ZEST, Subject characteristics.

Table 4. Subject Characteristics[#]

		Zoster vaccine (N=11 211)		Placebo (N=11 228)	
		No.	%	No.	%
Gender	Male	4 298	38.3	4 256	37.9
	Female	6913	61.7	6972	62.1
Race	White	10 588	94.4	10 601	94.4
	Black or African American	468	4.2	476	4.2
	Asian	80	0.7	68	0.6
	Other [a]	75	0.7	83	0.7
Mean age ± SD [y]		54.9 ± 6 2.8		54.8 ± 6 2.8	

Abbreviation: SD, standard deviation.
[a] *Other includes American Indian or Alaska Native, Multiracial, Native Hawaiian or Other Pacific Islander.*

[#]**Source:** *Adapted from Schmader KE, Levin MJ, Gnann JW Jr, et al. Efficacy, Safety, and Tolerability of Herpes Zoster Vaccine in Persons Aged 50-59 Years. Clin Infect Dis 2012;54(7):922-8.*

Ad table 1-III.

D: ZEST (NCT 00534248), In- and exclusion criteria*.

- **Eligibility:**

1) Ages eligible for study: 50 years to 59 years
2) Genders eligible for study: both
3) Accepts healthy volunteers: yes

Inclusion Criteria:

1) Must be between 50 - 59 years of age
2) No fever on day of vaccination
3) Females of reproductive potential must be willing to use acceptable form of birth control

Exclusion Criteria:

1) Have received chicken pox or shingles vaccine
2) Have already had shingles
3) Have recently had another vaccination
4) Pregnant or breast feeding. Have participated in another research study in the last 30 days
5) You are taking certain antiviral drugs
6) History of allergic reaction to any vaccine component, including gelatin or neomycin

Sponsors and Collaborators:

Merck

* **Source:** *Adapted from Schmader KE, Levin MJ, Gnann JW Jr, et al. Efficacy, Safety, and Tolerability of Herpes Zoster Vaccine in Persons Aged 50-59 Years. Clin Infect Dis 2012;54(7):922-8.*

Risk of bias tables

Internal validity describes the extent to which the (treatment) difference observed in a trial (or a meta-analysis) is likely to reflect the 'true' effect within the trial (or in the trial population) by considering methodological quality criteria. Because the 'truth' can never be assessed, it is more appropriate to speak of the potential for or risk of bias.

The Cochrane Handbook for Systematic Reviews of Interventions specifies 7 relevant domains for the assessment of the risk of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.

The risk of bias should be assessed on 2 levels, i.e. firstly, on a (general) study level, and secondly, on an outcome level. The risk of bias is categorized into 3 groups: low risk of bias, high risk of bias, and unclear risk of bias. There are at least 4 options to deal with the risk of bias: (i) rely only on studies with a low risk of bias; (ii) perform sensitivity analyses according to the different risk of bias categories; (iii) describe the uncertainty with regard to the different levels of risk of bias, so that subsequent decisions can be made considering this uncertainty; (iv) combine option (ii) and (iii).

For guidance see EUnetHTA guideline 'Internal validity of randomized controlled trials'.

Table 5: Risk of bias – study level

Trial	Adequate generation of randomization sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician			
SPS	Unclear (no further details on randomization)	Yes	Yes	Yes	Yes	Unclear	Low
Adverse Event Substudy of the SPS	No (participants in the sub-study were not randomly selected.	Yes	Yes	Yes	Yes	Unclear	High (participants not randomly selected)
ZEST	Yes	Yes	Yes	Yes	Yes	Unclear	Low

Table 6: Risk of bias – outcome level: summarised assessment

Outcome	Study level	Overall survival (mortality)	Incidences		Pain			Health-related quality of life	Adverse events		
Trial▼			Herpes zoster	Post herpetic neuralgia	Duration	severity	ADL		[AE]	[SAE]	[Treatment discont. due to AEs]
SPS (incl. substudy)	High	L	L	L	L	H[4]	H[5]	H[6]	L	L	L
ZEST	High	L	L	n.a.	L	H[7]	n.a.	n.a.	L	L[8]	L
comments: H= High risk; L=Low risk; n.a.= not assessed. Comments: outcomes denoted as high risk are discussed below (notes).											

[4] no specific data available about pain severity; patient reported outcome (PRO).
[5] ZBPI is not validated to older people. ZIQ does, but data were not shown. It was mentioned by the authors of the article that the data were similar, but is was not shown.
[6] VAS and SF12 are both not specific for HZ. Euroqol VAS is validated, but data is not shown. It was mentioned that the data were similar. SF12 is validated in the US, mean 50 years old.
[7] Description of pain severity is poorly described. {Every 3 days during the 21-day period following rash onset, subjects were asked to rate their acute HZ-related pain (least, average, worst) in the prior 24 hours on a 0 (no pain) to 10 (worst pain imaginable) rating scale using the Zoster Brief Pain Inventory (ZBPI), a validated measure of HZ-related pain.} Also patient reported outcome.
[8] SAE is not defined in the paper itself, but can be found in the supplementary appendix and the clinical protocol of the study.

Table 7: Risk of bias – outcome level

Outcome Trial	**Risk of bias – study level**	**Blinding – outcome assessors**	**ITT* principle adequately realized**	**Selective outcome reporting unlikely**	**No other aspects according to risk of bias**	**Risk of bias – outcome level**
Overall survival (mortality)						
SPS, including substudy	Low	Low	Yes (Low)	Low	Low	Low
ZEST	Low	low	Yes (Low)	Low	Low	Low
Incidence						
SPS, including substudy	Low	Low	Yes (Low)	No (high)[9]	Low	high
ZEST	Low	Low	Yes (Low)	No (high)9	Low	high
Pain9						
SPS, including substudy	High	High	Yes (Low)	No (high)	unclear#	High
ZEST	High	High	Yes (Low)	No (high)	unclear#	High
comments: * Both studies performed 2 intention-to-treat (ITT) analyses: with all individuals developing HZ (ITT) and only with those who developed HZ after 30 days from the vaccine injection (modified ITT). # unclear due to the high risks of other parameters.						

[9] PHN is pain related; pain assessement is a patient reported outcome.

Applicability tables

For guidance see guideline 'Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals'.

The aim of the guideline on applicability is to assess whether there is a relevant effect modification when a specific intervention is applied to the population of interest. To assess the relative effectiveness of interventions, trials with a pragmatic approach which have more 'noise of practice', are more suitable than trials with an explanatory approach that are conducted within a strict trials setting. Regardless of the availability of such information the likeliness that the available evidence is applicable to the decision problems should be indicated.

Methods

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other:

Critical appraisal criteria:

The applicability of individual studies was assessed using the four step process developed by

Atkins et al. (2011):

Step 1. Determine the most important factors that may affect applicability
Step 2. Systematically abstract and report key characteristics that may affect applicability in evidence tables (highlight studies with a pragmatic approach and data on effect size of effect modification).
Step 3. Make and report judgements about major limitations to applicability of individual studies.
Step 4. Consider and summarize the applicability of a body of evidence

Method of synthesis

The results of step 1, 2 and 4 were tabulated.

Results

Table 8. Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The target population includes immune competent individuals of 50 years or older. In clinical studies vaccine efficacy was investigated in adults 60 years of age or older [Oxman 2005] and aged 50–59 years. Immunocompromised persons were excluded both in the Shingles Prevention Study [Oxman 2005] and ZEST [Schmader 2012]. No published data or subgroup analysis is available for people over 80 years in RCT. Data of 80+ is provided by MAH. Real world data is reported in [Langan 2013, Tseng 2011]. Data on individuals aged ≥65 years enrolled in Medicare are reported. Vaccine efficacy about the incidence of herpes zoster is estimated for all the sample and for each age groups (65-69, 70-74, 75-79, ≥ 80). The risk of off label use isn't discussed. Patients with one or more

	contra indication will probably also be vaccinated in the daily practice.
Intervention	**Formulation:** EMA approved the refrigerated formulation of Zostavax, while a frozen formulation also existed. The last one is authorized in US. In the Shingles Prevention Study [Oxman 2005] the frozen formulation was used. Relevant is the data reported in [Gilderman 2008]. In this RCT, the safety and the immunogenicity of a refrigerator-stable formulation of Zostavax (44,846 PFU/0.65 ml) is compared to the frozen formulation (56,845 PFU/0.65 ml) in persons >50 years of age. **Potency:** EMA requires that 1 dose (0.65 ml) of Zostavax contains a minimum of 19,400 PFUs (plaque forming units), which corresponds to the minimum potency at expiry (end of shelf life).Higher potencies are necessary at release of the lots to take into account potency loss within the 18 month-shelf life time. In the Shingles Prevention Study [Oxman 2005] the median estimated potency of the zoster vaccine at vaccination was 24,600 PFU. In the same study, more than 90% of vaccinated participants received doses lower than 32,300 PFU. This means that the RCT of [Oxman 2005] considered a zoster vaccine with a different potency than the one approved now. **HZ detection criteria:** Furthermore, criteria as described in the Shingles Prevention Study [Oxman 2005] to detect HZ doesn't correspond to real clinical practice. DNA is not always extracted from clinical specimens obtained from patients suspected of having HZ. **Appropriateness of use:** In the clinical practice it's expected to be more difficult to monitor inappropriate use of Zostavax in case of contraindication or not studied co-medications. **Expired vaccine:** Professionals (doctors or nurses) should pay attention to vaccine expiry date in order to avoid inappropriate use of the vaccine.
Comparators	No comments.
Outcomes	**Burden of illness:** The primary endpoint in the SPS was the burden of illness (BOI) due to herpes zoster (HZ), a measure affected by the incidence, severity, and duration of the associated pain and discomfort [Oxman 2005]. According to the EUnetHTA guidelines, the presentation of the composite endpoints as such is not sufficient; the individual components within the composite endpoint should be reported, too. It is unclear whether the reduction in the BOI was caused by a reduction in the incidence, duration of the pain, intensity of the pain or a combination of these parameters. A problem with this method is that small differences in HZ pain-related measures over a long period of time can have a large effect on this score but may not be clinically meaningful. This would lead to an overestimate of vaccine effectiveness. **Pain assessment**: Pain assessment in the clinical practice is expected to be not comparable to the methods used in [Oxman 2005] and [Schmader 2010]. The Zoster Brief Pain Inventory (ZBPI), the EuroQol visual analog scale (VAS) and the Medical Outcomes Study 12-item Short Form Survey (SF- 12) are the criteria followed in RCT. All these are patient reported outcomes. VAS and SF-12 are not specific for HZ.

	[Fried 2010] discussed in his publication about the complexity of the method to summarize the effect of HZ over time. It is not clear what the clinical meaning is of this HZ pain-related measures. The criteria used could lead to an overestimation of vaccine effectiveness. Indeed, in the SPS, persons whose HZ pain level dropped below 3 on a scale from 0 to 10 on two consecutive weekly queries were no longer queried as regularly, and their subsequent scores were imputed as 0. **Follow up duration:** Zostavax is studied in the subgroup of participants ≥60 years till 10 years post-vaccination [Oxman 2005], and in the subgroup 50 to 59 years up to 2 years post-vaccination [Schmader 2012]. Because Zostavax is used as a prevention, the intended population is large and otherwise not ill. Long-term safety data is therefore extra needed. It's required also for the definition of long-term duration of protection. A study of long-term persistence of efficacy for up to 10 years post vaccination was conducted as part of pharmacovigilance activities required by EMA.
Setting	**Reimbursement options.** At national level the options are for: • a programmatic approach with the inclusion of the HZ vaccination in the National Immunisation Programme (NIP), publicly funded and organised after a full assessment performed by a national committee; • the inclusion of HZ vaccine in the reimbursement scheme allowing individual and free use of HZ vaccine; • no reimbursement for Zostavax **Off label use risks:** Zostavax off label use is possible. The risk of HZ development in people <50 years is limited (age-specific HZ incidence rates are at around 1/1 000 in children <10 years, 2/1 000 in adults aged < 40 years, around 1–4/1 000 in adults aged 40–50 years [Pinchinat 2013]). Furthermore, Zostavax could also be administered to immunocompromised patients.

APPENDIX 2: RESULT CARDS

HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

[A0002]: What is the disease or health condition in the scope of this assessment?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☒
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

Herpes Zoster (HZ) and Herpes Zoster-related Post Herpetic Neuralgia (PHN) are target conditions under assessment. The assessment covers as well ophthalmic HZ or Herpes Zoster Ophthalmicus (HZO), which is HZ involving the ophthalmic division of the trigeminal nerve.

Herpes zoster (HZ), or shingles, results from reactivation of the varicella zoster virus (VZV) which has remained latent in sensory ganglia following primary infection i.e. varicella or chickenpox. In few cases, VZV could be subclinical or exceedingly mild in nature (about 5%): HZ can only occur in people who have had chickenpox and cannot be asymptomatic. Infectious VZV is found in vesicles of patients with zoster and varicella, but virus shed in the absence of disease has not been documented apart in special patient categories. Furthermore herpes zoster may occur in HIV-infected persons who are otherwise asymptomatic, in that case serologic testing may be appropriate in patients without apparent risk factors for shingles (e.g., healthy persons who are younger than 50 years of age).

VZV is a herpes virus that causes two distinct diseases: varicella and HZ. The first usually occurs in childhood and is highly contagious [Guenther 2006]. Because almost all European adults are VZV-positive they are potential at-risk to develop HZ. It is not possible to predict who will develop HZ, when and how severe the disease will be [Centres for Disease Control and Prevention 2008].

HZ is a localized, generally painful cutaneous eruption that occurs most frequently among older adults and immunocompromised persons [Centres for Disease Control and Prevention 2008].
Acute HZ involves VZV replication and spread in the dorsal root or cranial ganglion and peripheral sensory nerve. Local spread may extend to dorsal roots and spinal cord and the virus may disseminate via the blood. A response leads to anatomical and functional damage to neural tissue in peripheral nerve, dorsal root ganglion and spinal cord, resulting in the onset of neuropathic pain and sensory abnormalities in the affected dermatome. As the virus reaches the dermis and epidermis, inflammation and blistering of the skin occur [Johnson 2004].

Patients with HZ can only transmit the virus to a susceptible contact (i.e. VZV-seronegative) causing varicella. HZ is not contracted from individuals with varicella or HZ [Johnson 2004].

Post-herpetic neuralgia (PHN) is the most common debilitating complication of HZ. PHN is a neuropathic pain syndrome, defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system [International Association for the Study of Pain 1994]. PHN is defined as a chronic long-lasting HZ-related pain occurring or persisting at least 1 or 3 or 4 months after the HZ rash or pain onset. No agreement exists on the

time frame to adopt. Current trends seem to prefer for PHN a 3 month after the HZ rash or pain onset lasting pain.

The exact pathophysiology of PHN remains unclear. Multiple mechanisms are at work in PHN pathophysiology. Two are the prevailing models. In the first one, peripheral nerve injury caused by VZV reactivation produces hyperexcitable nociceptors that have a lower activation threshold for stimuli. This may lead to increase excitability of central nociceptors in the dorsal horn of the spinal cord. While in the second model, degeneration of nociceptive neurons causes central sensitization [Johnson 2007].

Older age is a well-established risk factor for the development of PHN in individuals with HZ, although severity of acute pain and rash at presentation have also been recognised as major risk factors.

Although uncommon, serious neurologic complications of HZ include encephalitis, stroke, aseptic meningitis, diaphragmatic paralysis, peripheral and cranial nerve palsies, Ramsay Hunt syndrome, delayed contralateral hemiplegia or encephalitis [Gershon 2006; Opstelten 2005].

Generally, HZ occurs only once in an individual's lifetime, however, it has been reported that immunocompetent persons may suffer from one or more episodes of HZ [Schmader 2008].

Discussion

Herpes zoster (HZ; shingles), results from reactivation of the varicella zoster virus (VZV) which has remained latent in sensory ganglia following primary infection i.e. varicella or chickenpox. Post-herpetic neuralgia (PHN) is the most common debilitating complication of HZ. PHN is a neuropathic pain syndrome, defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐

Partly ☒
Not ☐

[A0003]: What are the known risk factors for the condition?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other: use also Table 2 to document

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

The Table summarizes the most important risk factors for herpes zoster. An important risk factor is previous varicella zoster virus (VZV) infection because herpes zoster can only occur in individuals who have previously had chickenpox.

Risk factors HZ	Reference
Varicella zoster virus (VZV) infection	CDCP 2008; Thomas 2004
Prodromal neuralgia (risk factor only for PHN)	Johnson 2007; Ragozzino 1982; Opstelten 2002; Gross 2003
Age	Jung 2004; Thomas 2004; CDCP 2008; Gialloreti 2010; Schmader 2008; Parruti 2010
Female gender	Opstelten 2006; Thomas 2004; Gialloreti 2010; Parruti 2010
Psychological stress	Gilden 2011; Thomas 2004
Trauma	Thomas 2004; Parruti 2010; Serino 2011
White race	Thomas 2004
Chronic conditions	Joesoef 2012; Di Legami 2007; Serino 2011
Skin infections	Yawn 2007
Immunosuppression	Guenther 2006; Gialloreti 2010; CDCP 2008; Schmader 2008; Gnann 2002; Thomas 2004 ¸Di Legami 2007
Surgical intervention	Parruti 2010
Smoking	Parruti 2010; Serino 2011
Tumour	Guenther 2006; Di Legami 2007; Schmader 2008; Gnann 2002

The risk of HZ increased significantly in presence of chronic conditions. They include allergic rhinitis, chronic obstructive pulmonary disease, coronary artery disease, depression, diabetes mellitus (4.5% [Di Legami 2007] and 17.4% [Serino 2011]), gout, hyperlipidemia, hypertension, hypothyroidism and osteoarthritis [Joesoef 2012]. Chronic cardiovascular diseases occur in 54.7% of patients while chronic respiratory diseases in 12.6% [Serino 2011].

The main risk factors of PHN is the age and in particular the patients >60 years old [Johnson 2007; de Moragas 1975] and severity of acute pain and severity of the rash at presentation [Gershon 2006; Whitley 1998; Jung 2004; Johnson 2007].

Who will suffer the most from the condition?

The herpes zoster affects mainly individuals over 50 years old [Joesoef 2012]. HZ is uncommon in children and young adults. In fact, it occurs in less than 10% of children [Guenther 2006]. Children under 12 are rarely affected unless immunosuppressed or infected as infants.

The incidence of herpes zoster increases with age [CDCP 2008] (See A0002). Indeed, age-specific HZ incidence rates are at around 1/1 000 in children <10 years, 2/1 000 in adults aged < 40 years, around 1-4/1 000 in adults aged 40-50 years.[Pinchinat 2013].

A sharp increase after 50 years is reported in many studies. For age specific incidence rate after 50 year see A0006.

The risk for zoster is elevated in immunocompromised persons [Lin 2010; Johnson 2007]. The rates of incidence are 29.4–51.5 per 1000 person years [Brisson 2003].

People with inflammatory diseases and rheumatoid arthritis are at high risk of developing HZ [Johnson 2007].

HZ is more common in women than men and is more than 10% in the age group > 60 years [Chidicac 2001; Thomas 2004]. Zoster occurs in 55% of women and in 45% of men [Hope Simpson 1975].

PHN affects 50% of patients over 60 years of age and 75% in those greater than 75 years of age [Guenther 2006; Johnson 2007]. PHN occurs in patients with severe acute pain and rash. PHN occurred in 18% of adult patients with HZ and in 33% of those aged 79 years and older [Yawn 2007].

Discussion

HZ can only occur in people who have had prior infection with varicella zoster virus. The risk of developing herpes zoster increases with age, in particular in the patients >50 years old. 15% of people with 80 years of age had experienced at least one episode of shingles and 50% of persons at 85 years have experienced zoster. VZV reactivation is associated with the age-related decline in cell-mediated immunity and therefore occurs more frequently in older adults. VZV-specific memory T-cell (CMI) have been shown to decline with age, and significantly from the age of 50 years old. Female gender has an increased risk factor of contracting HZ in the 25-64 year old age groups. The increase depends on a biological mechanism by which women are more susceptible to VZV reactivation. Other risk factors for herpes zoster (HZ) are immunosuppression (such as a HIV infection) and tumours. Stroke, trauma, psychological stress and chronic conditions are most common in patients with HZ.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

[A0004]: What is the natural course of the condition?

What is the natural course of the condition?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other: use also Table 2 to document

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

Herpes zoster is a disease that results from reactivation of a latent infection of the varicella zoster virus (VZV). The reactivation of VZV usually results in a vesicular skin rash that is localized in one, two or three dermatomes [Chua 2010]. The virus can reactivate 40-50 years after infection with VZV [Finnerup 2005 de Moragas 1957]. After a few years of infection with varicella, the virus can get out of the neurons and causes the rash. VZV can become latent in the sensory ganglia of the nerve. It usually occurs on the chest or abdomen, more rarely on the face and particularly on the trigeminal [Kimberlin 2007]. HZ primarily affects adult patients whose immune system is severely compromised [Burke 1982; Johnson 2007].

HZ begins when VZV replicates and spreads within the ganglion, causing pain [Gnann 2002; Schmader 2008]. During the reactivation of VZV, the the sensory ganglia are sites of viral replication, with subsequent destruction of neurons and satellite cells [Kimberlin 2007]. This neurological damage starts before the rash appears [Arvin 2005]. Before the appearance of the zoster rash, VZV travels along the affected sensory nerves to the skin evading innate and adaptive immune responses to spread and ultimately produce the unilateral, vesicular dermatomal rash [Kimberlin 2007]. In the skin, the virus causes local inflammation and bubbles [Schmader 2008]. The pain in the short and long term caused by herpes zoster comes from the widespread growth of the virus in the infected nerves and causes inflammation [Schmader 2007].

Although the rash is the most distinctive feature of HZ, the most frequently debilitating symptom is neuropathic pain which may occur during a long period (> 3 months). Herpes zoster is characterized by three phases of acute pain: acute herpetic neuralgia, subacute herpetic neuralgia and post-herpetic neuralgia (PHN) [Johnson 2007]. These phases are described in A0005.

HZ is presented by a rash that lasts 2 to 4 weeks. The rash is almost always unilateral, maculopapular and is followed by the development of blisters that form crusts within 7-10 days [Johnson 2004]. The eruption occurs primarily in thoracic dermatomes and the eye. The rash can leave scars and pigmentation changes [Johnson 2007]. The eruption was characterized by erythema and vesicles, and 20% of patients also had scabs [Chidiac 2001].

The median duration of acute herpes zoster rash ranges from a minimum of 2-4 days [Chidiac 2001] to a maximum of 12 days [Di Legami 2007]. Pain was the initial manifestation in 74% of the patients, and the mean interval between the onset of pain and the appearance of skin lesions was 2 days [Chidiac 2001].

Discussion

Herpes zoster is caused by the varicella-zoster virus (VZV) and it manifests initially as a rash. Zoster can only occur in individuals who has previously infected with VZV (chickenpox). The immune system is able to eliminate the virus in most places in the body, but it remains latent in the sensory ganglia of the nerve. The latency of VZV is poorly understood. Indeed, there aren't methods to find the virus in the ganglia. The preventive effect of the zoster vaccine is thought to be a consequence of its boosting effect on an older person's cell-mediated immunity to VZV [Kimberlin 2007].

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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

[A0005]: What is the burden of disease for the patient?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☒
- Other: use also Table 2 to document

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

What are the symptoms and the burden of disease for the patient?

Although the rash is the most distinctive feature of HZ, the most frequently debilitating symptom is neuropathic pain which may occur during a long period (> 3 months). Herpes zoster is characterized by three phases of acute pain: acute herpetic neuralgia, subacute herpetic neuralgia and post-herpetic neuralgia (PHN).

Acute pain is manifested by a rash that lasts up to 4 weeks [Gershon 2006]. Acute phase of HZ is characterized by a unilateral and vesicular rash, most often accompanied by pain or discomfort [Drolet 2013]. The sub-acute herpetic phase refers to pain that persists beyond healing of the rash. It persists from 30 days to several months. Finally PHN is the phase chronic pain and refers to pain persisting beyond three months from the initial onset of the rash. It can last for many years [Gershon 2006; Jung 2004; Guenther 2006].

Several factors have been consistently identified as influencing the development of chronic pain: older age, greater rash severity and greater acute pain as well as the presence of prodromal pain and impact on functional status.

The duration of HZ-associated pain increases with age: patients over 50 years of age have a significantly higher risk of developing PHN than younger patients over time. The time of highest risk for PHN begins at 60 years of age [Schmader 2008].

The main symptoms of herpes zoster are summarized in the following table.

Symptoms HZ	References
Rash	Drolet 2013: Opstelten 2005; McKendrick 2009; Helgason 2000; Johnson 2007; Bouhassira 2012; Schmader 1999; Volpi 2008
Headache	Dworkin 2007; Johnson 2007; Cebrian Cuenca 2010; Schmader 1999; Wutzler 1997
Malaise	Dworkin 2007; Johnson 2007; Cebrian Cuenca 2010; Johnson 2004; Wutzler 1997
Paresthesia	Wutzler 1997; Goh 1997
Dysesthesia,	Cebrian Cuenca 2010
Fever	Dworkin 2007; Johnson 2007; Cebrian Cuenca 2010; Wutzler 1997; Goh 1997
Nausea	Wutzler 1997
Pruritus	Cebrian Cuenca 2010; Bouhassira 2012
Fatigue	Dworkin 2007
Burning pain	Katz 2004; Johnson 2004; Johnson 2010; Wutzler 1997; Goh 1997
Itching pain	Katz 2004; Johnson 2010; Petursson 1998; Bouhassira 2012; Goh 1997
Nocturnal sweating	Wutzler 1997
Maculopapular rash	Opstelten 2005; CDCP 2008; Drolet 2013; Petursson 1998
Vescicles	Opstelten 2005
Motor weakness	CDCP 2008
Depression	Goh 1997

The common symptoms are rash, itching (27%), depression (20%), paresthesia (12%), fever (12%), stabbing (15%) and shooting (15%) [Goh 1997]. Other symptoms are burning pain in 81,7% of the patients, headache in 38,9%, malaise in 44,9%, nocturnal sweating in 19,2% and nausea in 10,6% [Wutzler 1997]. The severity of pain decreases significantly during the first 30 days after rash onset, from an average of 6.3/10.0 to 2.4/10.0. The pain continues to decrease after 30 days [Drolet 2013].

PHN is characterized by constant or intermittent burning, itching or aching. Therefore the main symptom is pain. The pain may persist many months after the onset of rash and it causes lower quality of life. In particular it interferes with work, daily activities and social relationship. Other symptoms are numbness, tingling and allodynia [Johnson 2007; Volpi 2008; Johnson 2010]. Allodynia is one of the most debilitating component of the illness. Sleep disturbance, anorexia, weight loss, chronic fatigue and depression are other typical signs of PHN [Johnson 2007; Volpi 2008].

In ophthalmic zoster a symptom is the conjunctivitis that resolves within a week. Other symptoms are a redness with dilatation of the vessels and a red eye with the reduction of the corneal sensitivity. These symptoms can cause chronic ocular inflammation, loss of vision and debilitating pain [Opstelten 2005].

A symptom of zoster paresis is motor weakness in the distribution noncranial nerve. It occurs within 2-3 weeks after the onset of the rash and can involve upper or lower limbs.

The acute neuritis of HZ produces pain dermatome in many older adults. The symptoms of acute neuritis varied and can be confused with those of other diseases. A symptom may be pain in the chest that can be mistaken for a heart attack. Another symptom is pain in the muscle that can be confused with an injury. Other signs relate to tingling or numbness. It is important to make a correct diagnosis in order to identify the disease and to treat it.

What is the impact of HZ and PHN on the quality of life of the patient?

The impact of HZ on quality of life could be expressed of:

- interference on activities of daily living;
- pain measurement scales. In order to capture these HZ related effects on patients' life pain has been investigated through validated questionnaires and/or pain scales;
- health related quality of life assessment tools.

Pain and problems in performing usual activities are reported in 79.6 % of the patients with HZ [Bouhassira 2012; Drolet 2013]. While in [Weinke 2010].91% of patients with PHN and 73% of those with HZ experienced problems with daily activities, including work, studies, housework, family and leisure activities [Weinke 2010].

The dimension of daily life on which HZ interfere are:

- sleep and mood [CDCP 2008; Bouhassira 2012; Oster 2005; Jensen 2007; Schmader 2008];
- physical functioning and/or limitation of movement [Bouhassira 2012; Drolet 2013; Weinke 2010];
- social functioning.;
- depression and psychological distress [Katz 2004; Jensen 2007]. Indeed, the pain is accompanied in many cases by a state of depression and psychological distress [Katz 2004; Jensen 2007];
- productive work life [Drolet 2013]. HZ has a negative impact on productive work life with a mean absenteeism of 26-32 hours per employee [Drolet 2013]. In the 8 month study of [Scott 2006] a total of 307 workdays were lost by the patients, and another 52 by carers among the 70 cases of confirmed HZ. While in [Singhal 2011] about half (51%) reported missing work due to HZ, and about an equal percentage reported little or much worse productivity than usual due to HZ while at work. On average, age-adjusted absenteeism- and presenteeism-related work loss was estimated at 31.6 hours, and 84.4 hours, respectively, with a combined work loss of 116.0 hours per HZ episode in a working person of 50-64 years of age [Singhal 2011]. Data in [Singhal 2011] is based on a telephone survey to individuals with ≥1 insurance claim for HZ in the past year. In [Weinke 2010] of the 39% of interviewees who were employed while affected by HZ/PHN, 65% reported absence from work in the last year due to HZ. Most employed patients with PHN (70%) and HZ (64%) stopped work during the disease [Weinke 2010].

PHN can interfere with the ability to perform essential activities of daily living and may result in physical disability and a loss of independence [Johnson 2007]. The patients with PHN report lower scores of depression and anxiety than patients with HZ [Volpi 2008]. The mean scores of pain associated with PHN and HZ, respectively, are 7.1 and 6.2. Mean pain interference scores in patients with PHN versus HZ were highest for sleep (6.5 versus 4.9), normal work (6.1 versus 4.4) and mood (5.9 versus 4.4).

Generic pain measurement scales could be: verbal, numerical and visual analogue scales. In generic verbal rating scales some words describe the intensity of pain. In numerical rating scales, patients choose the number that best corresponds to the intensity of their pain (from 0 to 10 or 0 to 100). In the visual analogue scale, patients put a mark on the point which corresponds to the level of intensity of pain [Katz 1999].

In [Weinke 2010] patients with PHN had statistically significantly worse outcomes on every pain. Pain levels were considerable, with mean pain scores in all patients, patients with HZ and those with PHN, respectively, of 6.3, 6.2 and 7.1 on average, and 7.2, 7.0 and 8.2 at worst ($P<0.05$ for patients with HZ versus PHN). High levels of pain (score 8–10) on average and at worst were reported by greater proportions of patients with PHN than with HZ [Weinke 2010]. Analysis in [Weinke 2010] showed that, of the seven areas of pain assessed, general activity had the highest significant impact on QoL rating.

The HZ related pain can be assessed by specific questionnaires as:

- Zoster Brief Pain Inventory (ZBPI) [Coplan 2004]. The Zoster Brief Pain Inventory (ZBPI) is a zoster-specific modification of the Brief Pain Inventory (BPI) done by including discomfort in the area of shingles rash. The aim is to capture allodynia and unpleasant sensations that are not always characterized as pain. The ZBPI uses a 11-point Likert scale (0 to 10) to rate pain in 4 ways (worst, least, and average in the last 24 hours and now) [Schmader 2007]. As detailed in [Coplan 2004], ZBPI has adequate test-retest reliability and validity. The worst pain score on ZBPI is correlated strongly with interference with ADL and reduction in quality of life. The choice of the cutoff of ≥ 3 to measure the impact of interventions on HZ pain is due to kappa statistics results. Indeed, kappa statistic for a worst pain score of ≥ 3 had lower 95% confidence interval above 0.40 (critical value to

differentiate between poor and reasonable kappas) among patient whose HZ pain persist beyond 90 days after rash onset or development of PHN.;
- Neuropathic pain Symptom Inventory (NPSI) [Bouhassira 2012];
- Zoster Impact Questionnaire (ZIQ) [Coplan 2004].

In Zostavax's clinical studies the Zoster Brief Pain Inventory (ZBPI) was used to calculate an HZ Severity-of-Illness Score [Oxman 2005]. In [Oxman 2005] for each confirmed case of herpes zoster, responses to the "worst pain" question in the Zoster Brief Pain Inventory were used to calculate a herpes-zoster severity-of-illness score. The "herpes-zoster burden-of-illness score" represented the average severity of illness among all participants.

While health related quality of life can be analyzed through generic assessment tools:

- EQ-5D [Scott 2006; Bouhassira 2012; Oster 2005]. In the study of [Scott et al. 2006], the average score of EQ-5D is 0.43 while in the study of [Oster et al. 2005] the mean EQ-5D health index score was is 0.61. The improvement of quality was obtained after 4 weeks [Scott 2006]. Pain and Anxiety are the dimensions of EQ-5D that is most affected by HZ. Two thirds of the sample are moderately or extremely anxious or depressed [Scott 2006; Bouhassira 2012];
- Medical Outcome Study Short Form 36 (MOS SF 36) scales [Chidiac 2001]. In MOS SF 36, the lowest score of the scale is 41 (for vitality) and the maximum 72 (for social functioning). The lowest values are observed in the group with PHN. In the three months before the onset of symptoms, 40% of patients experienced a negative change in the personal and working life [Chidiac 2001]. HZ had the lowest score in almost all categories [McElhaney 2010]. At second week patients reported the worst quality of life for vitality, physical and emotional functioning [Lydick 1995].
- the 12-item short-form health survey (SF-12);
- the Hospital Anxiety and Depression scale [Bouhassira 2012].

Patients with PHN have a worse quality of life than those with HZ [Weinke 2010; Volpi 2008; McElhaney 2010]. In [Weinke 2010] greater proportions of patients with PHN than HZ reported that their QoL was affected to a high level (35% versus 17%) or medium level (50% versus 39%)

Discussion

HZ and PHN have a negative impact on physical, psychological, functional and social status of patients. The review of the literature reveals a strong relationship between pain and activities of daily living. Pain is one of the main symptoms of PHN and have both for HZ and PHN a strong impact on perceived QoL. Pain and anxiety are the dimensions of EQ-5D that is most affected by HZ. The mean scores of pain associated with PHN and HZ, respectively, are 7.1 and 6.2 [Weinke 2010]. Mean pain interference scores in patients with PHN versus HZ were highest for sleep (6.5 versus 4.9), normal work (6.1 versus 4.4) and mood (5.9 versus 4.4). Most employed patients with PHN (70%) and HZ (64%) stopped work during the disease [Weinke 2010].

In some studies [Schmader 2008; Jensen 2007; Johnson 2010] there was a correlation between the intensity of pain and quality of life. The greater intensity of the pain in HZ and PHN is associated to a lower quality of life, and particularly to an interference with daily activities.

In Zostavax's clinical studies the Zoster Brief Pain Inventory (ZBPI) were used to calculate an HZ Severity-of-Illness Score [Oxman 2005]. The worst pain score on ZBPI is correlated strongly with interference with ADL and reduction in quality of life.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

[A0006]: What is the burden of the disease for society?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other: use also Table 2 to document

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

What is the incidence of the diseases (HZ and PHN)?

What is the mortality due to HZ?

Incidence of HZ in Europe is estimated around 3-4 per 1000 person-years. It highly age dependent.
Recent studies conducted in Europe estimate an overall annual incidence of HZ of 2.0-4.6 cases per 1000 persons [Pinchinat 2013]. HZ incidence rates appeared to increase rapidly after 50 years to around 7–8/1 000 up to 10/1 000 at 80 years of age and older. According to a US large retrospective population study [Yawn 2007] incidence ranges from 4.2 per 1000 person-years in people aged 50 to 59 years and 10.7 per 1000 person-years in people aged 80+ years.

Country specific data are available for Belgium, France, Germany, Iceland, Italy, the Netherlands, Spain, Switzerland and UK. For each of these countries available data on HZ, PHN incidence and mortality as well as gender and age differences are reported below. At the end a table compares country HZ incidences.

Belgium:

- **Herpes Zoster:** An annual incidence of 4.57/1000 person year (95% CI 4.31-4.79) is reported. HZ is more common in women (4.84 /1000 person year (4.5-5.19) incidence) respect to men (4.27/1000 person year (3.9-4.56) in men). Incidence varies from 0.6% per 1000 person year (age group till 4 year) to a peak incidence of 9 per 1000 person year in the group of 75 plus [Truyers 2005, Pichinat 2013].
- **Post Herpetic Neuralgia:** Data non available.
- **Herpes Zoster Ophthalmicus:** Data non available.
- **Mortality:** Data non available.

France:

- **Herpes Zoster:** The yearly HZ incidence rate averaged 382 cases per 100,000 inhabitants (95% CI 364–405) [Chiappe 2010]. Incidence increases with age. Incidence per 100,000 inhabitants increases from 416 (95% CI 385-454) in the age group 45-54 to 868 (95% CI 689-1051) in the age group 65-74 till reaching 1077 (95% CI 895-1350) in the group 85-94 years old. Females represented 57.7% of HZ cases (95% CI 55.6–59.7). The age-adjusted relative risk of HZ for females versus males was 1.15 (95% CI 1.12–1.18, $p < 0.05$).
  The overall percentage of reported HZ cases with an associated immunodepression condition was 4.7% (95% CI 3.8–5.6%) [Chiappe 2010].
  According to a study conducted via a representative sample of French Physicians [Mick 2010], the annual incidence of herpes zoster is estimated at 8.99/1000 (95% CI 8.34–9.64) for people aged 50 years and above. Incidence increases from 5.54/1000 (95% CI 5.01-6.67) in the age group 50-60 to 13.47/1000 (95% CI 11.26-15.68) for people ≥ 80 years old.
- **Post Herpetic Neuralgia:** Post-herpetic neuralgia (PHN) data is not included in the Sentinelles network questionnaire [Chiappe 2010]. Anyway, 12-month, longitudinal, prospective, multicenter observational study was conducted in primary care in France [Bouhassira 2012]. PHN is more common in patients older than 70 years old (52% versus 48%) and in females (55.1% versus 44.9%).
  While according to [Mick 2010] 32.1% and 17.6% of patients presented PHN at 3 and 6 months.

- **Herpes Zoster Ophthalmicus:** HZ ophthalmicus amounted to 6.5% of the reported cases (95% CI 5.2–7.8%). This proportion peaked for cases occurring in persons ≥85 years old (13.1%, p < 0.005) [Chiappe 2010].
  In [Czernichow 2001] 8% of patients reported ophthalmic complications.
- **Mortality:** Herpes zoster mortality was assessed through the French National Mortality Database (INSERM CepiDC) for deaths between 2000-2007 in [Chiappe 2010]. An average of 176±13 HZ-related deaths per year were recorded. The average HZ mortality rate per year was 0.29±0.04 per 100,000 inhabitants when considering all deaths including an HZ code. It was 0.11±0.03 per 100,000 inhabitants when only considering death certificates with a primary HZ diagnosis. For HZ as a primary diagnosis, the age-specific mortality rate was 0.03±0.01 per 100,000 for the ≤64 years age group and 4.36±0.20 per 100,000 for the ≥65 years age group, among whom 96.8% of deaths occurred.

The following table summarises data available per age groups for France [Chiappe 2010].

Age groups (years)	Incidence per 100,000 inhabitants (range)	Mortality per 100,000 inhabitants (95% CI)
45-54	416 (385-454)	0.0031 (0-0.069)
55-64	577 (497-696)	0.072 (0.009-0.135)
65-74	868 (689-1051)	0.236 (0.102-0.370)
75-84	985 (862-1046)	1.25 (0.90-1.60)
85-94	1077 (895-1350)	7.24 (5.66-8.82)
>94	1437 (0-2485)	19.48 (11.50-27.47)

Source: *Adapted from Chiappe SG, Sarazin M, Turbelin C, et al. Herpes zoster:Burden of disease in France. Vaccine 2010;28(50):7933-8.*

Germany:

- **Herpes Zoster:** In [Ultsch 2011] emerged a HZ-incidence of 9.6/1,000 person years in people ≥50 years old. HZ-incidence increased by age from 6.21 in people 50-54 years to 13.19 per 1,000 PY in people aged ≥ 90 years. Females were significantly more frequently affected than males in terms of outpatient HZ-incidence (11.12 versus 7.8 per 1,000 PY). The age-dependency of the incidence existed in both genders.
  In [Schiffner-Rohe 2010]the overall observed incidence rate of herpes zoster in people ≥50 year was 9.4 cases per 1,000 person-years (PY). Incidence rate rose with age: from 6.8 per 1,000 PY in 50 -54 year-olds to 12.4 PY in persons 80 years and older. Incidence rate in the immunocompromised was higher (11.6 per 1,000 PY) than in the immunocompetent (9.1 per 1,000 PY).
- **Post Herpetic Neuralgia:** a prospective survey of physicians reported that 28% of HZ cases (all ages) developed PHN (defined as pain 4-5 weeks after crusting) [Meister 1998]. In [Ultsch 2011] PHN-incidence was estimated to range between 0.43 and 1.33 per 1,000 person years.
  In [Schiffner-Rohe 2010] 10.1% of herpes-zoster-patients suffered after 1 month of PHN, 6.9% had at least 3 months of PHN.
- **Herpes Zoster Ophthalmicus:** In [Meister 1998] Zoster Ophthalmicus occurred in 0.87% of visits. In [Ultsch 2011] HZ with ocular involvement was reported in approximately 4% of HZ-cases.
- **Mortality:** mortality increased with age from 0.02/100,000 (age-group 50-54) to 3.86/100,000 (age-group ≥90 years). Mortality is higher in women (0.29 versus 0.10 per 100,000 PY).

The following table summarises data available per age groups (with 95% CI) for Germany [Ultsch 2011].

Age groups (years)	Incidence per 1,000 PY	Mortality rate per 100,000 PY
50-54	6.21 (6.15-6.28)	0.02 (0.00-0.10)
55-59	7.59 (7.52-7.67)	0
60-64	8.94 (8.85-9.03)	0.02 (0.00-0.13)
65-69	10.70 (10.61-10.78)	0.06 (0.01-0.17)
70-74	11.34 (11.24-11.44)	0.11 (0.04-0.27)
75-79	12.15 (12.03-12.28)	0.30 (0.14-0.57)
80-84	12.53 (12.38-12.68)	0.54 (0.28-0.94)

85-89	12.58 (12.38-12.78)	1.20 (0.67-1.98)
90+	13.19 (12.88-13.51)	3.86 (2.36-5.96)
Total	9.60 (9.56-9.63)	0.21 (0.16-0.26)

Source: *Adapted from Ultsch B, Siedler A, Rieck T, et al. Herpes zoster in Germany: Quantifying the burden of disease. BMC Infect Dis 2011;11:173.*

Iceland:

- **Herpes Zoster:** A prospective cohort study was conducted [Helgason 2000] on patients with a first episode of zoster. Age was a significant predictor of pain at each time point after zoster and also a significant predictor of severity of pain at one month (P = 0.02) and duration of pain (P < 0.001).
- **Post Herpetic Neuralgia:** Among patients younger than 60 years, the risk of PHN three months after the start of the zoster rash was 1.8% (95% CI 0.59%- 4.18%) [Helgason 2000]. Gender was not a predictor of postherpetic neuralgia.
- **Herpes Zoster Ophthalmicus:** : Data non available
- **Mortality**: Data non available

Italy:

- **Herpes Zoster:** A study was conducted at regional level (Piedmont Region) on the population over 14 years old followed by GPs [Di Legami 2007]. A total incidence of 1.74 cases/1000 population was estimated. It ranged from 1.15/1000 person years (95% CI 0.53-2.18) in the age group 45-64 years to 5.78/1000 person years (95% CI 3.53-8.92) for people older than 74 years.
  A retrospective, population-based study was conducted in 4 regions on people aged ≥50 years. The incidence was 4.31per 1000 person-years (95% CI: 4.11-4.52) for whole population and 4.07 per 1000 person-years (95% CI: 3.88-4.27) for the immunocompetent adults. Incidence increased with age, with the peak for the age group 75-79 years [Gialloreti 2010].
- **Post Herpetic Neuralgia:** For PHN incidence in immunocompetent patients was 9.4% (95% CI: 8.2-10.7) and 7.2% (95% CI: 6.2-8.2) at 1 and 3 months, respectively. The PHN proportions were similar for all HZ patients aged ≥50 years at 1 and 3 months: 10.0% (95% CI: 8.8-11.2) and 7.7% (95% CI: 6.6-8.8) [Gialloreti 2010]. PHN was more common in women [Gialloreti 2010]. In the adult population, the proportion of women versus men with HZ who developed PHN was 8.9% (95% CI: 7.7-10.2) versus 6.6% (95% CI: 5.5-7.7) for PHN at 1 month and 6.9% (95% CI: 5.8-8.0) versus 5.1% (95% CI: 4.1-6.1) for PHN at 3 months.
- **Herpes Zoster Ophthalmicus:** According to the first study conducted in Italy on HZ [di Luzio Paparatti 1999] ocular complications occurred in 5.7% of cases. They were assessed in 19.8% of patients suffering of cranical HZ.
- **Mortality:** Data non available.

The following table summarises data available per age groups for Italy [Gialloreti 2010].

	Incidence per 1,000 PY		% PHN 1 month		% PHN 3 months	
Age groups	All	Immunocompetent	All	Immunocompetent	All	Immunocompetent
50-54	4.15	4.00	4.8	4.9	4.3	4.4
55-59	5.63	5.47	3.8	3.1	3.4	3.0
60-64	6.90	6.61	6.6	6.2	5.3	4.7
65-69	7.11	6.75	9.3	8.5	7.2	6.3
70-74	8.22	7.68	12.2	12.6	9.5	9.1
75-79	8.56	8.06	14.0	14.5	10.7	11.3
80-84	7.97	7.69	16.0	15.7	12.0	11.3
85+	6.13	5.85	14.9	13.4	11.3	10.2

Source: *Adapted from Gialloreti LE, Merito M, Pezzotti P, et al. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: A retrospective, population-based study. BMC Infect Dis 2010;10:230.*

The Netherlands:

- **Herpes Zoster:** The annual incidence of herpes zoster based on GP consultations amounted to 320–330 (average 325) per 100,000 in the period 1998–2001 [de Melker 2006]. According to a study focused on gender differences [Opstelten 2006], HZ incidence in females was 3.9/1000 patients/year (95% CI 3.6–4.2), and in males, 2.5/1000 patients/year (95% CI, 2.3–2.8).

- **Post Herpetic Neuralgia:** In a study conducted on general practice research database emerged a risk of developing PHN 1 month after HZ of 6.5% (95% 4.9-8.3), which increased to 11.7 (95% CI 8.5-14.9) for patients aged ≥ 55 years [Opstelten 2002]. Estimates for PHN at 3 moths were based on few cases. Anyway, the higher incidence was evident for patients older than 75 years (9.0%, 95% CI 4.8-15.2).
- **Herpes Zoster Ophthalmicus:** A significant association among PHN at 1 month and ophthalmic localization emerged in [Opstelten 2002] (OR 2.3, 95% CI 1.0-4.6).
- **Mortality**: On average 18 deaths per year were registered (range 13–26) for HZ. A linear increase of HZ death rate with age was identified. 97% of deaths attributable to HZ were observed in individuals aged 60 years and above [de Melker 2006].
  According to CBS figures death attributable to HZ in 2011 amount to 20. HZ mortality increase with age and reached it's peak in people older that 80 years. The following data reports in details mortality data for HZ provided by CBS.

Year Age group	50-55	55-60	60-65	65-70	70-75	75-80	80-85	85-90	90-95	>95 years	Total
2007	0	1	0	0	1	1	5	6	5	1	20
2008	0	0	0	1	0	0	6	3	3	1	14
2009	0	0	0	1	0	0	4	6	5	4	20
2010	0	1	1	0	1	1	2	7	7	5	25
2011	0	0	0	0	1	1	2	4	6	6	20
2007-2011	0	2	1	2	3	3	19	26	26	17	99
% per age group	0,00	2,02	1,01	2,02	3,03	3,03	19,19	26,26	26,26	17,17	100

Source: *Adapted from CBS. Doodsoorzaken; uitgebreide lijst, leeftijd en geslacht. Herpes Zoster. Available at: http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=7233&D1=90&D2=0&D3=0&D4=0,4,9,13-15&VW=T*

The following table summarises data available per age groups for Netherlands in published literature [Opstelten 2006] [Opstelten 2002]:

Age groups	Incidence per 100,000 PY [Opstelten 2006]	
	Female	Male
45-64	633	320
65-74	588	517
75+	857	780

Source: *Adapted from Opstelten W, van Essen GA, Schellevis F, et al. Gender as an independent risk factor for herpes zoster: a population-based prospective study. Ann Epidemiol 2006;16(9):692-5.*

Age groups	% PHN (95% CI) [Opstelten 2002]	
	1 month	3 months
45-54	3.9 (1.3-9.0)	0.8 (0.02-4.3)
55-64	36.5 (3.0-11.9)	2.9 (0.8-7.2)
65-74	10.7 (5.2-16.3)	3.3 (0.9-8.3)
75+	18.0 (11.5-24.6)	90 (4.8-15.2)

Source: *Adapted from Opstelten W, van Essen GA, Schellevis F, et al. Gender as an independent risk factor for herpes zoster: a population-based prospective study. Ann Epidemiol 2006;16(9):692-5.*

Spain:

- **Herpes Zoster:** A study conducted in Navarra Region reported an incidence for HZ of 4.15 cases per 1,000 inhabitants [Garcia Cenoz 2011]. It increased from 5.86 in age group 50-54 to 8.99 per 1,000 inhabitants for people older than 75 years. While in Valencia [Cebrian-Cuenca 2010] annual incidence of HZ was 4.1/1,000 individuals >14 years of age (95% CI 3.4-4.7). By age group the incidence of HZ was higher for patients 50-59 years of age (6.7/1,000 inhabitants (95% CI 4.4-9)) and in those ≥ 70 years of age (to 11.1/1,000 Inhabitants (95% CI 8.3-13.9)), compared to those patients aged from 60 to 69 years (annual incidence of 5.2/1000 inhabitants (95% CI 3-7.4)).
  The annual incidence was also higher in females (4.5/1,000 inhabitants; 95% CI 3.5-5.4) than it was in males (2.7/1,000 inhabitants; 95% CI 1.9-3.5; p = 0.005).
- **Post Herpetic Neuralgia:** Data non available

- **Herpes Zoster Ophthalmicus:** In [Cebrian-Cuenca 2010] 10% of cases reported Ophthalmic HZ, while ocular complications occurred in 8.5% of patients.
- **Mortality:** In [Gil 2009] focused on hospitalized HZ patient, the case-fatality rate was 4.6 % overall and of 7.2 % among patients >80 years old. The mortality rate was 0.6 per 100,000 people, being of 3.9 per 100,000 population among patients >80 years old.

The following table summarises data available per age groups for Spain [Garcia Cenoz 2011];

Age groups (years)	Incidence per 1,000 inhabitants
50-54	5.86
55-59	6.64
60-64	8.41
65-69	9.05
70-74	9.6
75+	8.99

Source: *Adapted from Garcia Cenoz M, Castilla J, Montes Y, et al. Varicella and herpes zoster incidence prior to the introduction of systematic child vaccination in Navarre, 2005-2006. An Sist Sanit Navar 2011;30:71-80.*

Switzerland:

- **Herpes Zoster:** Incidence is relatively stable up to 49 years (118-155/100'000 on average over 4 years) then increases quickly and continuously with the age (817/100'000 among the ≥ 90-year olds) [Richard 2010].
- **Post Herpetic Neuralgia:** Data non available
- **Herpes Zoster Ophthalmicus:** Data non available
- **Mortality:** Data non available

UK:

- **Herpes Zoster:** The average incidence rates for zoster between 1991 and 2000 was 373 per 100,000 years It increased to over 900 cases per 100,000 person-years in those aged 65 years or greater [Brisson 2003].
  A retrospective analysis of the UK General Practice Research Database on people ≥ 50 years estimated an incidence of 5.23/1000 person-years. The incidence rate ranged from 3.44/1000 person years in those 50-54 years old, to 7.29/1000 person years in people in the age group 80-84 year. While in older patients (≥85 years) it was slightly lower (6.22/1000 person-years).
  Differences among gender were investigated in [Fleming 2004].
- **Post Herpetic Neuralgia:** Respectively 19.5% and 13.7% of patients developed PHN at least 1 and 3 months after HZ diagnosis [Gauthier 2008]. Quite similar the result in [Scott 2006] where PHN at 3 months occurred in 13.4% of patients.
  Herpes Zoster Ophthalmicus: In [van Hoek 2009] was reported that in 10–20% of cases there is an ophthalmic localisation of the zoster rash.
- **Mortality:** Mortality data were extracted from the Office of National Statistics (2001–2005) database in [van Hoek 2009]. Mortality due to herpes zoster is low until the age of 85 (0–0.5 deaths per 100,000 per years), and then it increases to 4.3 per 100,000 per year. This corresponds to a case fatality rate of 0.36% in the oldest age group.

The following table summarises data available per age groups for Italy [Gauthier 2008]:

Age groups (years)	Incidence per 1,000 inhabitants	% PHN 1 month	% PHN 3 months
50-54	3.44	10	8
55-59	4.08	14	10
60-64	4.90	16	11
65-69	5.96	19	13
70-74	6.34	2	15
75-79	7.09	27	18
80-84	7.29	29	21
85+	6.22	26	19

Source: *Adapted from Gauthier A, Breuer J, Carrington D, et al. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. Epidemiol Infect 2008;137:38-47.*

Incidence in specific risk groups

The incidence of herpes zoster (HZ) is 10–20 times higher in patients infected with human immunodeficiency virus (HIV) than in age-matched HIV-negative persons [Moanna 2013]. The annual incidence in that group of patients decreased significantly from 6.3 episodes in 1987 to 1.0 episode per 100 person-years in 2011. HAART therapy is associated with a lower incidence of HZ compared not-HAART-therapy patients (3.56 versus 4.22) [Moanna 2013]. Apart from antiretroviral therapy, age plays a role on incidence of HZ. HIV patients differ from general population given that the incidence of HZ decreased with increasing age [Moanna 2013]. A longitudinal study demonstrated an incidence of 29.4 cases of herpes zoster per 1000 person-years among HIV-seropositive persons, as compared with 2.0 cases per 1000 person-years among HIV-seronegative controls [Gnann 2002]. The risk of HZ was higher in the general population (9.80/1 000 in Germany and 4.31/1 000 in Italy) than among immunocompetent people (9.50/1 000 in Germany and 4.07/1 000 in Italy) [Pinchinat 2013]. In Italy, 5675 incident cases of HZ were documented in adults over 3 years, of which 3620 occurred in immunocompetent patients aged ≥50 years (incidence of 6.31 per 1000 person-years) [Gialloreti 2010].

In order to have an overall pictures, the following table summarises available data on HZ incidence in European countries:

Country	Study dates	Age criteria	Incidence /1000 PY (95% CI)	Reference
Belgium	1994-2003	All	4.57 (4.31-4.79)	Truyers 2005, Pinchinat 2013
France	2009	All	5.52 (5.06-5.98)	Pinchinat 2013
France	2005-2008	All	3.82 (3.64-4.05)	Chiappe 2010, Pinchinat 2013
France	2005	≥50 y	8.99 (8.34-9.64)	Mick 2010, Pinchinat 2013
France	1998	All	3.20 (3.00-3.40)	Czernichow 2001, Pinchinat 2013
Germany	2004	≥50 y	9.80 (9.20-10.40)	Schiffner-Rohe 2010, Pinchinat 2013
Germany	1992-1993	All	2.26	Pinchinat 2013
Germany	2007-2008	≥50 y	9.6	Ultsch 2011
Iceland	1990-1995	All	2.00 (1.80-2.20)	Helgason 2000, Pinchinat 2013
Italy	2003-2005	≥15 y	4.31 (4.11-4.52)	Gialloreti 2010, Pinchinat 2013
Italy	2004	≥14 y	1.74 (1.28-2.32)	Di Legami 2007, Pinchinat 2013
Netherlands	2001	All	3.20 (3.00-3.40)	Opstelten 2006, Pinchinat 2013
Netherlands	1998-2001	All	3.25	de Melker 2006, Pinchinat 2013
Netherlands	1994-1999	All	3.40 (2.90-3.90)	Opstelten 2002, Pinchinat 2013
Spain	2007	> 14 y	4.10 (3.40-4.70)	Cebrian-Cuenca 2010, Pinchinat 2013
Spain	2005-2006	All	4.15	Garcia Cenoz 2011, Pinchinat 2013
Switzerland	1998-2001	All	2.36	Richard 2010, Pinchinat 2013
UK	2000-2006	≥50 y	5.23 (2.17-5.29)	Gauthier 2008, Pinchinat 2013
UK	1947-1972	All	3.40	Pinchinat 2013
UK	1994-2001	All	3.20	Fleming 2004, Pinchinat 2013
UK	1991-2000	All	3.73	Brisson 2003, Pinchinat 2013

Hospitalisation rates for HZ and PHN

HZ infection and its complications, especially PHN are associated with high rates of health care utilization, for outpatient visits and prescription of drugs, but also leads to hospitalisations in several cases. Morbidity and mortality increase markedly with age.

In European countries, several studies have been conducted to assess health care resource use caused by HZ and PHN management. Their methodologies differ which makes international comparisons quite difficult.

Country specific data is available for Belgium, France, Germany, Italy, the Netherlands, Spain, and UK. For each of these countries available data on hospitalisation due to HZ and PHN are reported below.

Belgium

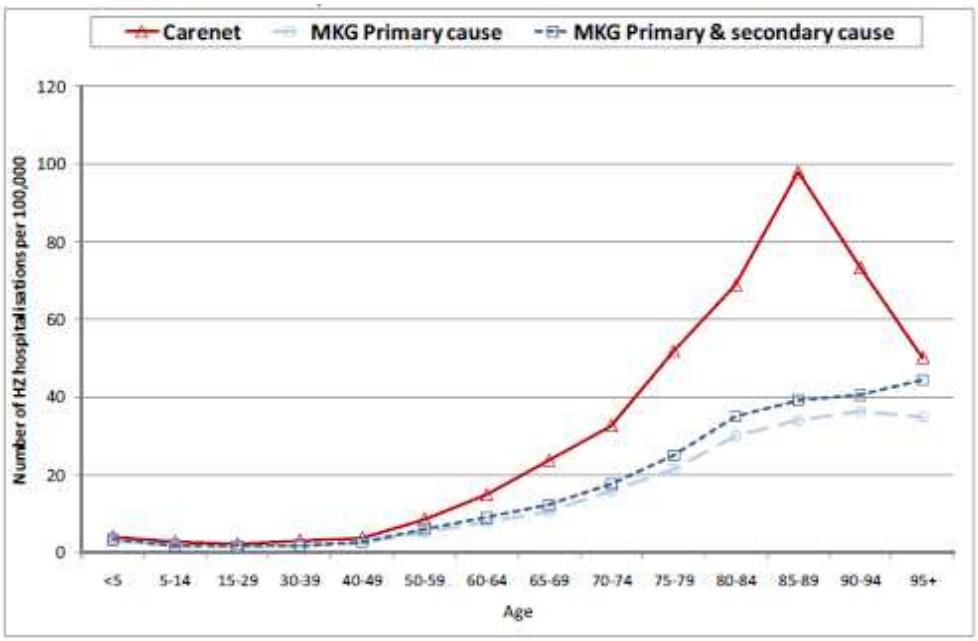
- **HZ:** Data available in reported in [Bilcke 2012] and [KCE 2010]. In [Bilcke 2012]. estimates are based on the national hospitalisation database

available for years 2000 up to 2007. **In** [Bilcke 2012].the average HZ hospitalisation rate is 14,2/100,000 person-years A representative survey among HZ hospitalized patients in Belgium [Bilcke 2012] showed that 10.5% of these patients did not visit a general practitioner for HZ, but were either admitted directly through the emergency department or referred to the hospital through a specialist doctor, or are hospitalized for another reason and got HZ in the hospital.

Additional estimates are available in [KCE 2010]. In that report, the HZ hospitalisation rates derived from the NCSF member population in the Carenet database and the MCD database differ significantly, especially for the older age groups. No explanation of that difference is reported. See graph below.

- **PHN: No available data**

The following graph reports hospitalisation rates of HZ per 100,000 according to two data sources available for Belgium [KCE 2010]



Source: *Reprinted from KCE report. Kosteneffectiviteit van vaccinatie tegen winkpokken bij kinderen en tegen zona bij ouderen in België. Health Technology Assessment (HTA). Bruxelles, 2010. KCE Reports 151A.* Copyright with permission from KCE.

France

- **HZ:** [Chiappe 2010] reported results of a national surveillance system of HZ set up in France in 2005. Hospitalisation data were collected by reviewing all hospital discharge reports containing a HZ code
- in [Chiappe 2010] the annual rates of hospitalisations and mortality due to HZ varied from 4.14±0.32 to 14.42±0.39 per 100,000 inhabitants depending on whether HZ was coded in a 'primary' or 'primary or associated' diagnosis (including both immunocompetent and immunocompromised). Immunodepression could be drug induced or not [Chiappe 2010]. One or more factors of immunodepression occurred in 43.4% of hospitalized cases. A higher rate of hospitalisation, according to GPs, was reported for immunodepressed people compared to non-immunodepressed people (11.0% and 0.8%, respectively) ($p < 0.05$). According to gender, the annual hospitalisation rate for HZ with a primary or associated diagnosis was 14.92±0.43 per 100,000 females versus 13.61±0.42 per 100,000 males ($p < 0.005$). Stratified by age, for females and males, the relative risk for hospitalisation with primary and associated HZ diagnoses amounted to 0.79 per 100,000 (95% CI 0.73–0.84) for the ≤64 years age group and 1.06 per 100,000 (95% CI 1.01–1.12) for the ≥65 years age group ($p < 0.001$). For all hospitalisations, the mean age was 72±0.43 years.

  The average length of stay was 8.1±0.1 days for hospitalisations with HZ as the primary diagnosis and 10.0±0.1 days for hospitalisations with HZ as an associated code [Chiappe 2010].

- **PHN: No available data**
  The following table summaries data available per age groups for France [Chiappe 2010].

Age groups (years)	Hospitalisation per 100,000 inhabitants (95% CI)	Average no. of hospitalisation for HZ ophtalmicus
45-54	10.48 (9.88-11.10)	70.1
55-64	14.39 (13.70-15.10)	117.1
65-74	34.03 (32.96-35.11)	188.6
75-84	57.30 (55.90-58.70)	27.0
85-94	105.9 (104.0-107.8)	178.4
>94	84.07 (82.37-85.76)	14.7

Source: *Adapted from Chiappe SG, Sarazin M, Turbelin C, et al. Herpes zoster:Burden of disease in France. Vaccine 2010;28(50):7933-8.*

Germany

- **HZ:** Data available is reported in [Ultsch 2011] and is based on the Federal Health Monitoring System (FHM). In [Ultsch 2011], incidence of HZ-associated hospitalisation increased from 0.13 to 1.08 per 1,000 PY from the age-group of 50-54 years to the age-group of 90+ years,. Of hospitalized HZ-cases aged ≥ 50 years 62% were female. The incidence of HZ leading to hospitalisation was 0.51 per 1,000 PY in females and 0.38 in males.
  [Ultsch 2011] reported a HZ-incidence of outpatient visits of 9.6/1,000 person years. Females were significantly more frequently affected than males in terms of outpatient HZ-incidence (11.12 versus 7.8 per 1,000 PY), inpatient HZ-incidence (0.51 versus 0.38 per 1,000 PY) and mortality (0.29 versus 0.10 per 100,000 PY).
- **PHN: No available data.**

The following table summarises data available per age groups (with 95% CI) for Germany [Ultsch 2011]:

Age groups	Hospitalisation incidence per 1,000 PY
50-54	0.13 (0.12-0.14)
55-59	0.20 (0.18-0.21)
60-64	0.31 (0.29-0.32)
65-69	0.44 (0.42-0.46)
70-74	0.55 (0.53-0.57)
75-79	0.79 (0.76-0.82)
80-84	0.99 (0.95-1.03)
85-89	1.07 (1.01-1.13)
90+	1.08 (0.99-1.17)
Total	0.45 (0.44-0.45)

Source: *Adapted from Ultsch B, Siedler A, Rieck T, et al. Herpes zoster in Germany: Quantifying the burden of disease. BMC Infect Dis 2011;11:173.*

Italy

- **HZ:** Data available is reported in [Gialloreti 2010]: Over the 3-year study period (2003-2005) [Gialloreti 2010], HZ or PHN as a primary diagnosis was responsible for 2,829 hospitalisations annually among the immunocompetent adult population, of which 2611 (92.3%) admissions were in those aged ≥50 years. The average incidences of hospitalisation for HZ and PHN were 4.61 per 100,000 person-years for a primary diagnosis and 7.94 per 100,000 person-years for primary and secondary diagnoses combined in immunocompetent population aged ≥50. Half of all HZ/PHN-related hospitalisations were in immunocompetent population. When primary and secondary diagnoses are combined, about 1.3% of HZ cases in Italy result in hospitalisation. Overall, 16.9% of HZ-related hospitalisations were due specifically to PHN. Rates increased progressively for each decade up to 85. In patients aged ≥50 years, mean stay was 7.8 ± 5.4 days for HZ.
- **PHN:** 2% of PHN cases required inpatient care [Gialloreti 2010]. The average incidences of hospitalisation for PHN was 0.94 per 100,000 person-years for a primary diagnosis and 1.66 per 100,000 person-years for primary and secondary diagnoses combined in immunocompetent population aged ≥50. When primary

and secondary diagnoses are combined, about 2% of PHN cases in Italy result in hospitalisation.

In patients aged ≥50 years, mean stay was 10.2 ± 8.6 days for PHN.[Gialloreti 2010] reported that a patient suffering from PHN (aged 50 and more) has to visit the general practitioner 12 times on average and is referred in 3 cases out of 4 to a specialist causing 4 additional visits.

The following table summarises data available per age groups for Italy [Gialloreti 2010]:

Age groups (years)	Incidence for Hospitalisation per 100,000 PY	
	HZ	PHN
50-54	3.83	0.58
55-59	5.28	1.15
60-64	7.19	1.20
65-69	10.31	2.45
70-74	14.07	3.7
75-79	16.99	4.45
80-84	20.48	4.97
85+	21.55	4.99

Source: *Adapted from Gialloreti LE, Merito M, Pezzotti P, et al. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: A retrospective, population-based study. BMC Infect Dis 2010;10:230.*

The Netherlands

- **HZ:** Data available is reported in [de Melker 2006].

The incidence of hospital admission due to herpes zoster was 2.7 (5.8 including side diagnosis) per 100,000, respectively [de Melker 2006].. The incidence of hospital admission increased with age from 50 to 54 years onwards. Both the annual number of hospital days and the average number of days per admission increases with increasing age, particularly from 70 years of age onwards [de Melker 2006].

The following table summarises data available per age groups for Netherlands [de Melker 2006]. Hospitalisation rate is per 100,000 and considers both main and side diagnosis for HZ, based on GP consultations.

Age groups (years)	Hospitalisation rate per 100,000
50-54	1.2
55-59	1.3
60-64	1.4
65-69	2.1
70-74	2.8
75-79	4.5
80-84	5.9
85+	5.3

Source: *Adapted from de Melker H, Berbers G, Hahne S, et al. The epidemiology of varicella and herpes zoster in The Netherlands:implications for varicella zoster virus vaccination. Vaccine 2006;24(18):3946-52.*

- **PHN:** No available data.
- **Additional data available:** [de Melker 2006] collected also data from the Dutch Institute of Primary Health Care, comprising 43 general practices. It shows that from 1998 to 2001, the average annual incidence of HZ consultations to general practitioners was 325 per 100,000, ranging from 390-547.5 per 100,000 for those age 50-59 years to 835 per 100,000 for those age ≥85 years [de Melker 2006]. The incidence was for all years higher for women (355 per 100,000) compared to men (290 per 100,000).

Spain

- **HZ:** In [Gil 2009] are reported results of a population-based retrospective epidemiological study to estimate the burden of herpes zoster requiring hospitalisation in Spain. Over a 7-year period (1998-2004), annually there were 13.4 hospitalisations for herpes zoster per 100,000 population in patients ≥ 30 years of age. The rate increases with age reaching a maximum in persons >80 years of age (54.3 admissions per 100,000 population >80 years of age). The case-fatality rate during hospitalisation was 4.6 % during the study period, being of 7.2 % among patients >80 years old. The mortality rate was 0.6 per 100,000

population, being of 3.9 per 100,000 population among patients >80 years old. The average length of stay in hospital was 12.9 days (SD 14.6).

The following table summarises data available per age groups for Spain [Gil 2009]:

Age groups (years)	Hospitalisation rates per 100,000 (95% CI)	Average length of stay (days, SD)
50-59	7.44 (7.14-7.75)	13.00 (16.41)
60-69	16.56 (16.07-17.04)	13.49 (16.52)
70-79	32.87 (32.12-33.62)	12.90 (13.57)
80+	54.33 (52.95-55.70)	12.59 (12.36)

Herpes zoster code was the first listed diagnosis in 27 % of the discharges. In the other 73 %, the primary cause of hospitalisation (first listed diagnosis) was mainly respiratory diseases (24%) and cardiovascular diseases (19%). Complications related with herpes zoster were present in 45% of admissions and neurological complications (28.6%) were the most frequently documented conditions in all age groups.

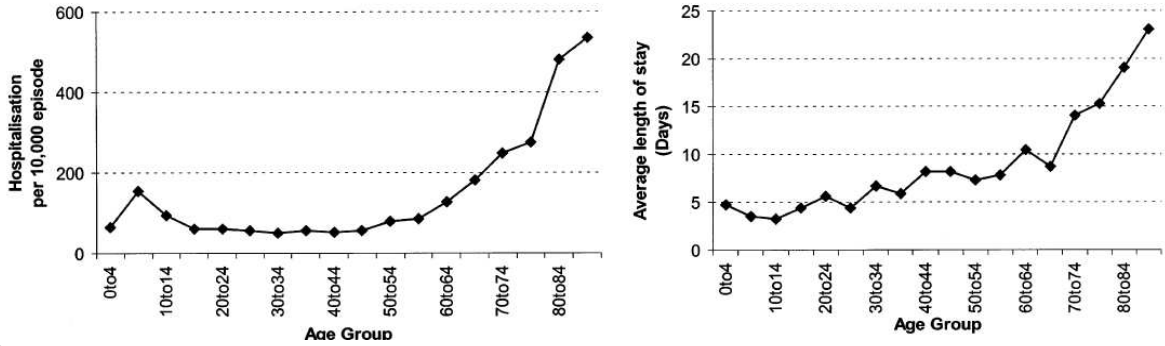
A Spanish study focused on immunocompetent population aged ≥50 years analyses data available for the period 1998- 2004 [Gil-Prieto 2011]. Around 2,300 hospitalisations were annually reported. Of these, 69.4% were aged ≥70 years, 20.4% were aged 60- 69 years and 10.2% were aged 50-59 years. The mean length of hospital stay was 12.4 days (SD 13.5), with a hospital fatality rate of 3.7% and a mean estimated cost per patient of 3,675€. Of the cases, 97.1% had another diagnosis at discharge in addition to HZ; of these, 60.8% had diabetes, COPD and/or chronic cardiovascular disease.

In HZ patients aged 50-59 years, the highest hospital mortality rate was observed in patients presenting COPD; the death rate was almost 4 times higher in this group compared with patients without chronic disease. In patients aged 60-69 and ≥ 70 years, mortality rates were 2 and 2.2 times higher, respectively in patients with HZ and cardiovascular disease than patients without these chronic conditions.

- **PHN:** No available data.

UK

- **HZ:** Data available is reported in [Gauthier 2008], [Brisson 2003] and [Edmunds 2001]. In [Gauthier 2008] main datasources were UK General Practice Research Database (GPRD) and Hospital Episode Statistics. In [Gauthier 2008] HZ caused 2074 hospitalisations during the study period in England (mean length of stay 9.9 days). [Gauthier 2008]. [Brisson 2003] analysed data from the Hospitalisation Episode Statistics and the Royal College of General Practitioners Weekly Returns Service. In [Brisson 2003] the overall zoster hospitalisation rate was 4.4 per 100,000 person-years in England during 1995/96. 69% of hospitalisations were in adults older than 65 years [Brisson 2003]**.** The average number of inpatient days per zoster admission also increases with age to 14 days in the elderly (over 65 years). Overall, 2% of all admissions due to zoster resulted in death in hospital, 4% of which were in patients with an underlying condition.[Brisson 2003]. Elderly adults who develop zoster are twelve times more likely to be hospitalised than children. In [Edmunds 2001]. the average length of stay for hospitalised cases also increases with age, from less than 5 days in children to greater than 20 days in the oldest age groups.
  The following graph reported hospitalisation rates and average length of stay per age group [Edmunds 2001]:



Source: *Reprinted from Vaccine 2001;19(23-24):3076-90 ; Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. Copyright© with permission from Elsevier Limited.*

- **PHN:** In [Gauthier 2008] the number of hospitalisations for PHN was estimated to be 756 (mean length of stay 11.2 days).11% of hospitalised cases of zoster also had a diagnostic code for PHN in [Edmunds 2001]. The average length of stay for these patients was not significantly different to the average length of stay of patients without a code for PHN in all age groups.
- **Additional data available:** In [Gauthier 2008].patients had on average 1.4 GP visits (S.D.=1.2) due to HZ. Only 2.9% of patients had records of secondary-care visits, mainly to ophthalmologists and physiotherapists**.**

Burden of disease on a population level measured in QALYs

Although there are not much data available on total number QALYs lost, some studies show that for instance the annual QALY loss due to HZ in individuals 50 years and older in Germany may be estimated to range between 3,065 and 24,094 [Ultsch 2011]. Another study estimates for England and Wales that the estimated overall QALYs lost due to VZV and HZ is 18000, 80% of which are due to HZ [Brisson 2003].

Discussion

Differences in age ranges, data sources (GPs, Sentinel networks etc), perspective (retrospective, prospective studies), coverage of the population, and time of follow up all make it difficult to compare epidemiological data between countries within Europe. These difficulties are also due to heterogeneity among surveillance systems for HZ. These data, where present, differs in terms of type (national mandatory or sentinel), the type of data collected (case-based or aggregated) and the reported case classification. Similar heterogeneity is present in published studies.

According to [Pichinat 2013] the overall incidence is lower in Iceland, Germany and Switzerland (around 2/1 000 PY), medium in the UK, the Netherlands and France (around 3/1 000 PY), and higher in Belgium, Spain and Italy (around 4/1 000 PY). Anyway no geographic trend of overall incidence is clearly observed.

A gender difference has been reported in several studies, with a higher incidence of HZ in women than men [Chiappe 2010, Ultsch 2011, de Melker 2006]. While incidence increases with age [Chiappe 2010, Ultsch 2011, Di Legami 2007, Garcia Cenon 2011, Richard 2010, Fleming 2004].

The incidence of herpes zoster (HZ) is 10–20 times higher in patients infected with human immunodeficiency virus (HIV) than in age-matched HIV-negative persons [Moanna 2013]. A longitudinal study demonstrated an incidence of 29.4 cases of herpes zoster per 1000 person-years among HIV-seropositive persons, as compared with 2.0 cases per 1000 person-years among HIV-seronegative controls [Gnann 2002].

The proportion of HZ patients reported to develop PHN varies across studies depending on the PHN definition used and the age of the study population. Methodological difference must be taken into account in comparing evidence. For instance, while in an Italian retropective study PHN resulted more common in women [Gialloreti 2010], in a prospective cohort study conducted in Iceland [Helganson 2000] emerged that gender is not a predictor of PHN development.

Overall, data on HZ-mortality are limited but trend to show that fatal cases are likely to be rare especially among immunocompetent/healthy people. In European countries, HZ is rarely recorded as the cause of death in patients under the age of 65. This might be different for the very old patients. Dutch mortality data for instance show a sharp increased in HZ mortality after the age of 80. Finally, HZ mortality rates reported in European studies do not allow always a split between immunocompetent and immunocompromised population. HZ ophthalmicus incidence ranges from 4% [Ultsch 2011], 5.7% [di Luzio Paparatti 1999], 6.5% [Chiappe 2010] to 10% in [Cebrian-Cuenca 2010]. It increases with age [Chiappe 2010]. In [Opstelten 2002] emerged an association between HZ ophthalmicus and PHN.

A comparison of health care resource use caused by HZ between countries is also difficult. Different are the data sources used. Hospital records or GP-interviews or databases were the main data sources. Indeed, patients could be admitted directly through the emergency department or referred to the hospital through a specialist doctor or via their GP [Bilcke 2012]. In hospital records HZ or PHN could appear as main or secondary (or associated) diagnosis [Chiappe 2010, Gialloreti 2010]. As a consequence hospitalisation rates differ. For instance, in France the annual rates of hospitalisations due to HZ varied from 4.14±0.32 to 14.42±0.39, depending on whether HZ was coded in a 'primary' or 'primary or associated' diagnosis [Chiappe 2010].

The incidences of hospitalisation for HZ or PHN should be integrated with an analysis of complications emerged during admission. That kind of data is reported in few studies [Gil 2009]. Few studies focused on immunocompetent population aged ≥50 years [Gialloreti 2010, Gil-Prieto 2011, Chiappe 2010]. In [Chiappe 2010] immunodepression factors occurred in 43.4% of hospitalized cases.

Both the annual number of hospital days and the average number of days per admission increases with increasing age, particularly from 70 years of age onwards [de Melker 2006, Gil 2009, Chiappe 2010, Ultsch 2011].

Higher hospitalisation rate are reported for female patient [Chiappe 2010, Ultsch 2011, de Melker 2006].

Length of stay is investigated as well. Average length of stay range from 8.1 days in [Chiappe 2010], 7.8 days in [Gialloreti 2012] to 12.9 days in [Gil 2009].

The case-fatality rate during hospitalisation is high in the age group 80+ reaching 7.2% [Gil 2009].

Few data is available on hospitalisation and PHN [Gialloretti 2010,Gauthier 2008]. Combining primary and secondary diagnoses about 2% of PHN cases in Italy result in hospitalisation [Gialloreti 2010] with a quite long length of stay (mean stay was 10.2 ± 8.6 days). In UK 11% of hospitalised cases of zoster also had a diagnostic code for PHN in [Edmunds 2001]. In [Gauthier 2008] a mean length of stay of 11.2 days was estimated, quite similar to the Italian data.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

[A0007]: What is the target population in this assessment?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other: use also Table 2 to document

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

HZ vaccine is indicated for immunization of individuals 50 years of age or older. The population eligible for zoster vaccination with Zostavax are the people aged 50 and more.

Not all of them are eligible for vaccination with Zostavax, as some immunocompromised groups are contraindicated [EMA Zostavax 2013]. To vaccination are excluded people:

- with hypersensitivity to the active substance, to any of the excipients or trace residuals (e.g. neomycin);
- with 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;
- having immunosuppressive therapy (including high-dose corticosteroids); however, ZOSTAVAX is not contraindicated for individuals receiving topical or inhaled corticosteroids, low-dose systemic corticosteroids, or patients who are receiving corticosteroids as replacement therapy (e.g. for adrenal insufficiency);
- with active untreated tuberculosis;
- who are pregnant.

The studied population is not exactly the same as the population approved by regulatory authorities, more groups of patient have been excluded from the trial. In the Shingles Prevention Study [Oxman 2005] eligible were adults 60 years of age or older with an history of varicella. Immunocompromised persons who might be at risk from the live attenuated zoster vaccine and might not have a normal immunologic response to it were excluded. As well were excluded persons with other conditions (e.g., chronic pain syndromes, cognitive impairment, severe hearing loss) that would interfere with the evaluation of herpes zoster.

Exclusion criteria included immunosuppression resulting from diseases or their treatment; prior HZ; prior zoster or varicella vaccination; hypersensitivity to components of the investigational vaccine/placebo; receipt of blood products within 3 months before randomization or planned during the study period; receipt of live vaccines within one month or inactivated vaccines within 2 weeks prior to randomization; concurrent antiviral therapy; or any condition that the investigator believed might interfere with the trial.

In [Schmader 2012] were enrolled healthy persons aged 50–59 years with a history of varicella or residence in a VZV-endemic area (an area in which chickenpox is a common childhood disease) for 30 years. Persons with immune compromise resulting from disease (eg, human immunodeficiency virus, cancer) or treatments(eg, corticosteroids, chemotherapy, transplant recipients) were excluded.

Discussion

The population eligible for zoster vaccination with ZOSTAVAX are the people aged 50 and more. At national level all population or just specific subgroups could be reimbursed or covered by national/local HZ vaccination programmes (See A0021). Zostavax is controindicated for immunocompromised patients. Acute and chronic leukaemias,

lymphoma, other conditions affecting the bone marrow or lymphatic system, immunosuppression due to HIV/AIDS, cellular immune deficiencies, are medical conditions incompatible with HZ vaccination as well as being under an immunosuppressive therapy (including high-dose corticosteroids).

In clinical studies vaccine efficacy was investigated in people adults 60 years of age or older and aged 50–59 years. Immunocompromised persons were excluded both in the Shingles Prevention Study [Oxman 2005] and in ZEST [Schmader 2012].

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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

[A0023]: How many people belong to the target population?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☒
- Other: use also Table 2 to document

Critical appraisal criteria Only official population estimates were considered.

Method of synthesis Narrative synthesis.

Result

The population eligible for zoster vaccination with ZOSTAVAX are the people aged 50 and more. The following table reports eligible population at country level for EU countries for which data is available on population at 1st January 2012 [EUROSTAT 2013].

In 2012 in EU-27, this population represented a total of 188 million people.[10]

[10] On 1 July 2013 Croatia became the 28th member of the European Union. In this assessment information about Croation are not incorporated,

European Union (27 countries)	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Total
	35.265.493	32.605.612	30.536.684	24.443.502	22.262.227	18.163.997	13.462.502	11.424.986	188.165.003
EU 27 countries:									
Austria	633.398	523.036	480.380	403.773	415.388	262.189	218.044	199.510	3.135.718
Belgium	792.678	716.159	648.904	522.222	433.486	396.675	312.325	260.226	4.082.675
Bulgaria	509.722	524.881	528.972	433.485	340.532	303.625	189.698	113.739	2.944.654
Cyprus	56.640	48.933	46.714	35.161	29.334	21.183	14.204	10.559	262.728
Czech Republic	649.679	745.595	743.740	595.116	402.749	307.188	234.820	161.563	3.840.450
Denmark	369.277	352.243	350.853	339.865	230.590	167.266	117.322	113.041	2.040.457
Estonia	93.804	87.421	79.541	57.251	65.348	47.873	35.990	23.788	491.016
Finland	371.613	383.809	395.223	296.656	239.251	180.510	144.120	119.103	2.130.285
France	4.349.411	4.173.865	4.118.154	2.957.137	2.370.694	2.257.722	1.834.383	1.762.879	23.824.245
Germany	6.422.953	5.550.054	4.898.241	4.039.543	5.001.255	3.438.528	2.367.684	2.033.540	33.751.798
Greece	786.800	720.462	661.683	575.427	541.376	513.849	363.228	229.167	4.391.992
Hungary	634.078	758.952	637.299	511.666	422.759	332.278	236.913	176.916	3.710.861
Ireland	277.097	246.826	219.246	179.159	132.088	103.038	70.716	59.927	1.288.097
Italy	4.248.533	3.788.281	3.759.210	3.175.225	3.121.173	2.539.990	1.975.398	1.744.258	24.352.068
Latvia	153.993	133.269	122.576	99.944	110.442	77.308	56.507	35.295	789.334
Lithuania	237.275	186.393	167.739	142.681	143.537	119.245	84.215	53.655	1.134.740
Luxembourg	37.597	31.757	26.319	20.633	17.625	14.497	11.841	8.665	168.934
Malta	30.486	29.287	30.447	24.186	16.074	13.382	8.529	6.569	158.960
Netherlands	1.216.443	1.104.542	1.070.490	874.056	649.753	506.544	368.582	317.433	6.107.843
Poland	2.848.818	2.916.642	2.471.547	1.459.742	1.328.316	1.146.666	834.494	555.797	13.562.022
Portugal	727.375	676.217	639.240	564.800	491.527	437.659	305.185	249.610	4.091.613
Romania	1.380.165	1.465.434	1.242.980	879.638	886.014	726.525	456.053	257.638	7.294.447
Slovenia	152.564	153.587	129.476	94.670	87.976	73.289	52.696	36.369	780.627
Spain	3.172.845	2.702.276	2.457.298	2.182.425	1.737.847	1.700.048	1.300.518	1.108.835	16.362.092
Sweden	584.502	574.437	597.421	578.463	401.432	306.555	244.891	253.327	3.541.028
United Kingdom	4.147.987	3.623.356	3.689.757	3.178.804	2.468.962	2.035.258	1.529.485	1.471.156	22.144.765

Other countries:	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Total
Belarus	778.969	646.080	537.432	294.500	392.498	288.718	206.728	115.118	3.260.043
Croatia	322.142	322.986	277.078	204.645	207.243	175.043	110.236	61.730	1.681.103
Former Yugoslav Republic of Macedonia, the	142.175	133.523	111.879	80.822	67.748	54.181	27.159	12.992	630.479
Georgia	324.979	271.506	225.552	124.710	202.438	135.868	92.986	59.847	1.437.886
Iceland	21.308	19.116	16.240	12.620	8.768	7.599	6.191	5.144	
Liechtenstein	2.915	2.527	2.260	1.869	1.333	887	588	559	12.938
Moldova	275.505	233.095	173.963	107.052	100.566	72.739	46.720	26.532	1.036.172
Montenegro	43.533	41.948	34.764	22.634	24.806	17.805	10.114	5.211	200.815
Norway	322.913	305.263	286.147	249.106	167.124	130.201	107.918	113.665	1.682.337
Serbia	511.621	580.623	506.178	322.386	336.314	286.873	175.918	100.867	2.820.780
Slovakia	379.760	387.898	323.234	221.774	176.699	135.107	94.661	62.421	1.781.554
Switzerland	582.357	499.696	457.353	411.009	312.450	259.407	197.484	184.802	2.904.558
Turkey	3.792.436	3.454.415	2.566.487	1.868.175	1.451.368	1.118.310	688.840	364.022	15.304.053
Ukraine	3.505.998	3.068.133	2.689.497	1.618.170	2.386.638	1.315.395	1.024.581	583.656	16.192.068

1

Discussion

The population eligible for zoster vaccination with ZOSTAVAX are the people aged 50 and more in 2012 in EU-27 countries represented a total of **188 million people**. Country specific demographic data are reported above.

It is difficult to assess accurately the number of people in each contraindicated group (See A0007). It is also not possible to predict who will develop HZ, when and how severe the disease will be [Centres for Disease Control and Prevention 2008]. As a result, it is not feasible to identify the target population exactly.

The most relevant contraindicated group is that of immunocompromised people.

According to published studies [Gialoretti 2010, Schiffner-Rohe 2009] and estimates of SPMSD, the proportions of people to be excluded from a ZOSTAVAX vaccination, due to contraindications are comprised between 7% and 11% of the ≥50 years population of the European countries.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

[A0011]: How much are the technologies utilised?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☒
- Other: use also Table 2 to document

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

There are no published data from Europe regarding the utilisation of this technology because this technology has not been used in the daily practice of the most European countries. Data from the USA, in which the vaccine has already been available for some time provide some information on the possible utilisation of this technology in the future.

A cohort study of 766,330 fully eligible individuals aged ≥65 years was undertaken in a 5% random sample of Medicare. These individuals received either zoster vaccination or nothing between 1st January 2007 and 31st December 2009 [Langan 2013].

Vaccine uptake was low (3.9%) especially in the oldest age group as total (1.5% in those aged 80 years old or greater), while vaccine had a higher uptake among woman (2.2% versus 2.0%) and among those with immune suppression (2.3% versus 2.1%). 140,925

individuals were immunosuppressed at some point during follow-up and 4,469 of these individuals were immunosuppressed at the time of herpes zoster vaccination.

In [Tseng 2011], beneficiaries aged 60 years or older of Kaiser Permanente Southern California (KPSC), who received herpes zoster vaccine from 2007-2009, were studied. According to that retrospective cohort study 25% of patients was vaccinated. Individuals in the vaccinated cohort were more likely to be white, to be women, and to have had a larger number of outpatient visits and a lower prevalence of chronic diseases.

Discussion

Because this technology has not been used in the daily practice of the most European countries no data from Europe were available. Two published studies reported real life data on a HZ vaccination program conducted in the USA [Langan 2013] [Tseng 2011]. Vaccine uptake was low in [Langan 2013] (3.9%) especially among older people (>80 years old), while in [Tseng 2011] a higher rate of uptake emerged (25%) especially among older people (>80 years old). Women and immunosuppressed people were more likely to take vaccination [Langan 2013]. The low uptake in the USA may be related to the problems with the production of the vaccine and the storage problems for the frozen version of the vaccine.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☐
Not ☒

[A0024]: How is the health condition currently diagnosed according to published guidelines and in practice?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☒
- Other: use also Table 2 to document

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

Important elements in establishing the diagnosis include: 1) painful or abnormal sensory prodrome; 2) dermatomal distribution; 3) grouped vesicles; 4) multiple sites filling the dermatome, especially where divisions of the sensory nerve are represented; 5) lack of history of a similar rash in the same distribution (to rule out recurrent zosteriform herpes simplex); and 6) pain and allodynia in the area of the rash [Dworkin 2007]. One

element that helps the diagnosis of HZ is the previous patient's exposure to VZV [CDCP 2008].

When the rash appears, the diagnosis is obvious [Schmader 1999]. But if the rash is not manifested, the diagnosis is more difficult. The condition that is most commonly mistaken for herpes zoster is herpes simplex virus infection [Cohen 2013]. In [Johnson 2007] is reported that in two studies, 20% of cases HZ was “confused” with herpes simplex. Differential diagnoses at this stage may include trauma, myocardial ischaemia, renal colic, gallbladder disease, dental pain or pleurisy [Johnson 2004]. In fact, HZ can be confused with other diseases, so it is very important to diagnose it in time to prevent/diminish the consequences of the disease. HZ can be confused with kidney stones, gallstones, or coronary artery disease as patients have localized pain or abnormal skin sensations [Yawn 2007]. Zoster may be confused with impetigo, contact dermatitis, folliculitis, scabies, insect bites, papular urticaria, candida infection, dermatitis herpetiformis, or drug rashes [CDCP 2008]. More frequently, zoster is confused with the eruption of herpes simplex virus (HSV), including eczema herpeticum [Oxman 2005].

HZ may be identified by laboratory tests [Gnann 2002]. The Tzanck test is useful for the diagnosis of acute infection with the herpes virus, but does not distinguish between herpes simplex virus and VZV. VZV can be identified through the use of tissue cultures. This test takes time and result requires several days. Direct fluorescent antibody (DFA) staining of VZV-infected cells in a scraping of cells from the base of the lesion is rapid and sensitive [CDCP 2008]. The direct immunofluorescence assay can distinguish herpes simplex virus infections from varicella–zoster virus infections [Gnann 2002]. Polymerase Chain reaction (PCR) is the most sensitive and specific test, but it is expensive. Besides, it takes at least 1 day to obtain results [Dworkin 2007]. PCR techniques are useful for detecting varicella–zoster virus DNA in fluid and tissues [Gnann 2002].

In [Sauerbrei 1999] PCR was compared with other diagnostic methods. The sensitivity and specificity of PCR for detecting VZV DNA were 95% and 100%, respectively, and these values for immunofluorescence testing for VZV antigen were 82% and 76% respectivey.

In the Shingles Prevention Study [Oxman 2005] each suspected case of HZ was classified as an "confirmed case of HZ" or "not a case of HZ", using a hierarchical algorithm that incorporated the results of the central PCR assay, local virus culture, and the final clinical diagnosis established by the study’s Clinical Evaluation Committee (CEC). The CEC, which consisted of five physicians, evaluated all suspected cases of HZ. For every suspected case of HZ, each CEC member provided a clinical diagnosis after independently reviewing a summary of the rash and pain evaluations, digital photographs of the subject's rash, and progress notes. The PCR assay was developed and validated to detect and discriminate between DNA from wild-type, vaccine strains of VZV and herpes simplex virus (HSV). Assay sensitivity was sufficient to detect approximately 13 copies of wild-type or vaccine strain VZV DNA. If the PCR assay revealed VZV DNA, the suspected case was classified as "a confirmed case of HZ". If the PCR assay was positive for HSV DNA or positive for gamma-globin DNA and negative for VZV DNA, the case was classified as "not a case of HZ".

Diagnosis of HZ can be problematic, particularly in the prodromal phase. In a survey of physicians practising in the UK [Hernry 1994], 53% admitted that diagnosis was difficult prior to rash formation, 47% had a delayed prescription because of their doubts in the diagnosis. Patient’s awareness of the symptoms associated with HZ is low and this may contribute to delayed presentation to primary care and subsequent diagnosis [Gershon 2006].

Discussion

Diagnosis of HZ in the prodromal period can be extremely difficult. The diagnosis can be facilitated by the appearance of rash and by questions to patient on clinical history. If the rash does not occur, it is very difficult to diagnose the disease because HZ related ts symptoms can be similar to those of other diseases. Incorrect diagnosis delays appropriate therapy resulting in reduction of the quality of life in patients. The diagnosis should be made as early as possible because antiviral therapy must be initiated within 72 hours of the onset of rash.

Tests to identify HZ are rarely used. Usually a skin sample is analyzed to check the presence of the virus. Laboratory tests may show an increase in white blood cells and antibodies to VZV (chickenpox virus).

Diagnosis criteria as followed in the Shingles Prevention Study [Oxman 2005] appear as quite uncommon in the real clinical practice. DNA is not also extracted from clinical specimens obtained from patients suspected of having HZ. Also a committee of 5 physicians with HZ expertise doesn't correspond to common practice.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

[A0025]: How is the health condition currently managed according to published guidelines and in practice?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other: use also Table 2 to document

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

The objectives of treating herpes zoster are to control acute pain, accelerate rash healing, minimize complications, reduce the risk of post-herpetic neuralgia (PHN) or other late appearing sequelae. An additional objective, important for immunosuppressed patients, is to reduce the risk of cutaneous and visceral dissemination of the varicella zoster virus (VZV) [Whitley 2010]. The diagnosis of HZ is generally evident at clinical presentation. Anyway, the clinical appearance of HZ may be preceded by prodromal symptoms (See A0024).

International consensus and country-specific guidelines exist. National guideline reflect the local specificities in terms of products' availabilities.

In the acute phase, antivirals are the mainstay treatment of HZ across Europe [Volpi 2005]. The main challenge of antiviral therapy is that, to be effective, treatment needs to be initiated within 72 hours of the onset of rash [Mounsey 2005]. That represents a major limitation. It's common that viral activity and neural damage are ongoing for several days before the diagnosis is made and treatment initiated [Volpi 2005].

Substantial differences in HZ management among European countries exist. In many cases, such as in Italy [Volpi 2005], patients seek medical advice at a late stage. A lack of recent official guidelines for HZ exists in many countries (France, Italy etc.). Austria refers to German guidelines [Gross 2003] that identifies as first choice systemic antiviral therapy. It's urgently indicated in patients beyond the age of 50 years and in patients at any age with herpes zoster in the head and neck area, especially in patients with zoster ophthalmicus. In Germany aciclovir, valaciclovir, famciclovir and brivudin are approved for the systemic antiviral treatment of herpes zoster. Appropriately dosed analgesics in combination with a neuroactive agent (such as amitriptylin) are very helpful when given together with antiviral therapy. The additive therapy with corticosteroids may shorten the degree and duration of acute zoster pain, but has no essential effect on the development of PHN. A pain expert is required in those cases.

Swiss guidelines [Forum Med Suisse 2007] require antiviral therapy with attention to contraindications.

UK guidelines support the use of oral antiviral drugs too. According to [Forbes 2012] 58% of incident zoster cases received an antiviral prescription. The majority (69.0%) were aciclovir. The proportion receiving antiviral prescriptions increased with age up to 65 years, then declined to 56.8% among patients aged ≥85 years. Antivirals were more commonly prescribed to immunosuppressed patients with HZ however they were not given routinely to this patient group [Forbes 2012].

In the Netherlands prescription of antiviral treatment to HZ patients seems to be less common. In [Opstelten 2005] only a minority of HZ patients (22.5%) were treated with antivirals. Increasing age (>75 years), ophthalmic localisation, presence of asthma/COPD, and adherence to professional guidelines were factors favouring prescription.

In France and Italy, aciclovir is utilized in 45.5% of the prescriptions, valaciclovir in 36.5%, brivudin in 9% and famciclovir in 9%. The other types of medication prescribed are analgesics (60.9%) and local adjuvant treatments (antiseptics and/or itch-relieving agents) [Chidiac 2001; Di Legami 2007]. Non-steroidal anti-inflammatory drug (NSAID) are prescribed in 67.9% of patients, opiate drug in 28.6% of the prescriptions, paracetamol in 3.5% and topical drugs represent 41.3% of prescriptions. 6.5% of patients received a combination of NSAID and opiate [Di Legami 2007].

Current International Herpes Management Forum (IHMF®) guidelines [Dworkin 2007] recommend that all patients with zoster ophthalmicus (HZO) presenting within 1 week of the rash onset should be offered oral antiviral therapy to reduce the incidence of ocular complications. The following options are mentioned: (a) aciclovir 800mg five times daily for 10 days; (b) valaciclovir 1000mg three times daily for 7 days; or (c) famciclovir 500mg three times daily for 7 days [Johnson 2001; Gnann 2002].

For HIV infected person the DHHS guidelines [DHHS 2013] and the Advisory Committee on Immunization Practices [ACIP] state that the administration of herpes zoster vaccine is not recommended.

To have a full picture of available HZ treatments, the following table summarizes the options with the approved dosage.

Treatment HZ	Dosage	Reference
Aciclovir	800 mg, five times daily for 7 days	Gershon 2006; Gnann 2002; Whitley 2010; Mounsey 2005; Volpi 2005; Gross 2003; Schmader 2001; Harkness 2011; Thakur 2012
Intravenous aciclovir	10 mg/kg, three times daily	Gershon 2006; Gross 2003
Valaciclovir	1000 mg, three times daily for 7 days	Gershon 2006; Gnann 2002; Tyring 2000; Whitley 2010; Mounsey 2005; Volpi 2005; Gross 2003; Schmader 2001; Harkness 2011; Thakur 2012
Brivudin	125 mg, once daily for 7 days	Gershon 2006; Di Legami 2007; Whitley 2010; Volpi 2005; Gross 2003;
Famciclovir	500 mg three times daily for 7 days	Gershon 2006; Gnann 2002;; Tyring 2000; Whitley 2010; Mounsey 2005; Volpi 2005; Schmader 2001; Harkness 2011; Thakur 2012
	250 mg three times daily for 7 days	Gershon 2006; Gross 2003
	750 mg once daily for 7 days	Gershon 2006;

Aciclovir, famciclovir, and valaciclovir are approved by the FDA for the treatment of herpes zoster [CDCP 2008; McKendrick 2009; Chidiac 2001; Johnson 2010; Bouhassira 2012; Insinga 2007; Johnson 2003]. These treatments reduce the duration of viral shedding and lesion formation, decrease the severity and duration of acute pain from zoster and the risk for progression to PHN [Gnann 2002; Li 2009; Tyring 2007]. According to [Li 2009], on the base of 12 randomised and quasi-randomised controlled trials, oral acyclovir did not reduce the incidence of PHN significantly. There is insufficient evidence to determine whether other antiviral treatments prevent PHN [Li 2009].

Four new drugs are being considered for the treatment of HZ: CMX001; a nucleoside analogue valomaciclovir (H2G); a helicase-primase inhibitor and two bicyclic nucleoside analogues (BCNAs) [Whitley 2010].

The following table synthetizes the treatments utilized in the management of patients with PHN.

Treatment PHN	Reference
Tricyclic antidepressants (TCA)	Mounsey 2005; Dworkin 2003; Oster 2005; Niv 2004; Johnson 2007; Raja 2002; Thakur 2012; Johnson 2009; Dworkin 2006; Gnann 2002; Rowbotham 1998; Finnerup 2005
Alpha-2-delta ligands	
Gabapentin	Mounsey 2005; Dworkin 2003; Niv 2004; Gilron 2005; Oster 2005; Tyring 2007; Schmader 2001; Johnson 2003; Dworkin 2007; Galluzzi 2007; Thakur 2012; Rowbotham 1998; Christo 2007; Gnann 2002; Scott 2006; Johnson 2007; Finnerup 2005
Pregabalin	Harkness 2011; Sabatowski 2004; Gilron 2005; Tyring 2007; Schmader 2001; Dworkin 2003; Johnson 2003; Dworkin 2007; Galluzzi 2007; Thakur 2012; Dworkin 2006; Christo 2007; Finnerup 2005
Opioids	Gnann 2002; Gilron 2005; Tyring 2007; Schmader 2001; Dworkin 2003; Johnson 2003; Dworkin 2007; Galluzzi 2007; Thakur 2012

Treatment PHN	Reference
Topical agents	
5% lidocaine patch	Khaliq 2007; Gilron 2005; Tyring 2007; Schmader 2001; Dworkin 2003; Johnson 2003; Dworkin 2007; Galluzzi 2007; Thakur 2012; Dworkin 2006; Christo 2007; Whitley 2010
Capsaicin cream	Gilron 2005; Tyring 2007; Schmader 2001; Dworkin 2003; Johnson 2003; Dworkin 2007; Galluzzi 2007; Thakur 2012; Christo 2007; Whitley 2010

Aciclovir, valaciclovir, famciclovir [Schmader 1999; Sacks 2013] and brivudin are also utilized in the treatments of PHN. Current treatments for postherpetic neuralgia are tricyclic antidepressant drugs (TCAs), alpha-2-delta ligands, opioids and topical agents.

TCAs are recommended in the treatment of first line. The drugs can relieve pain in less than half of the patients [Dworkin 2003]. The most common TCAs are amitriptyline, desipramine and clomipramine. These treatments are utilized in monotherapy or in combination with other medications [Rowbotham 1998]. Amitriptyline is the least expensive and most available tricyclic and has similar efficacy to other tricyclics but is more poorly tolerated than secondary amine agents such as nortriptyline [Dworkin 2003; Whitley 2010]. Anticonvulsant agents, tricyclic antidepressants, and other antidepressant agents were prescribed for 9.7%, 0.7%, and 0.4% of patients [Bouhassira 2012].

alpha-2-delta ligands include the anticonvulsants of first line: gabapentin and pregabalin. Gabapentin alleviates pain [Rowbotham 1998; Whitley 2010; Dworkin 2003] and sleep interference associated with PHN. Gabapentin and pregabalin (150–600 mg/day) can improve the quality of life in these patients [Dworkin 2003].

Topical agents include 5% lidocaine patch and capsaicin cream. These treatments show a reduction in pain of patients with PHN [Dworkin 2006; Guenther 2006; Whitley 2010].

Opioids, tricyclic antidepressants and gabapentin reduce the severity of postherpetic neuralgia [Gnann 2002]. Additional analgesia is required for most patients. Some can be treated with paracetamol alone, many require the addition of a weak opioid such as codeine and some will require strong analgesics such as axycodone or morphine [Johnson 2009].

Discussion

The guidelines [Dworkin 2006] recommend the use of oral antiviral agents for the treatment of herpes zoster. The effectiveness of treatment is achieved if treatment is started within 72 hours of the onset of acute symptoms. In a few cases, the therapy is started within 72 hours of the onset of acute symptoms because patients delay the medical visit or because the disease often manifests with unusual symptoms and it becomes difficult to be diagnosed by physicians. The management of patients with PHN is complicated. Drugs can reduce the duration and severity of pain,but it can not prevent the onset of PHN.

Current International Herpes Management Forum (IHMF®) guidelines [Dworkin 2006] recommend that all patients with zoster ophthalmicus (HZO) presenting within 1 week of the rash onset should be offered oral antiviral therapy with one of the following drugs to reduce the incidence of ocular complications: aciclovir; valaciclovir or famciclovir [Johnson 2001; Gnann 2002].

Substantial differences in HZ management among European countries exist. Furthermore, application of national guidelines is an issue. For istance, in the Netherlands prescription of antiviral treatment to HZ patients seems to be less common. In [Opstelten 2005] only a minority of HZ patients (22.5%) had a prescription for a antiviral treatment.

Tricyclic antidepressants, gabapentin, pregabalin and 5% lidocaine patch are recommended as first-line treatments for PHN in guidelines issued by the American Academy of Neurology (2004) , the International Association for the Study of Pain (2007), and the European Federation of Neurological Societies (2010). Opioids are considered a second-line or third-line therapy in British and Canadian guidelines [Nalamachu 2012].

For HIV infected person the DHHS guidelines [DHHS 2013] and the Advisory Committee on Immunization Practices [ACIP] state that the administration of herpes zoster vaccine is not recommended.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐

Partly ☒
Not ☐

[A0020]: What is the marketing authorisation status of the technology?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☒
- Other: use also Table 2 to document

Critical appraisal criteria: Only official documents on marketing authorization processes were considered. A search through the websites of the main Medicines Agencies was conducted.

The following websites were searched:

- EMA (European Medicines Agency)
- FDA (Food and Drug Administration)
- Health Canada.

Method of synthesis Narrative

Result

ZOSTAVAX was first authorized in Australia on 02-May-2006 (International Birth Date IBD). The vaccine was authorized in the EU on 19-May-2006 [EMA 2013] and in the USA on 25-May-2006 [FDA 2013], and the first launch worldwide was in the USA in June 2006. For Europe the initial registration on 19 May 2006 was for the frozen formulation and refrigerated form was approved in January 2007.

As of December 2012, ZOSTAVAX is registered in 54 countries (incl. European Union member states):

- North America: Canada, United States, Mexico;
- Latin America: Argentina*, Bolivia*, Brazil, Chile, Colombia, Peru*, Puerto Rico, Venezuela;
- Middle East & Africa: Israel, South Africa;
- Asia Pacific: Australia, Hong Kong, Korea, Macau, Malaysia, New Zealand, Singapore, Taiwan, Thailand*;
- Europe: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Latvia, Liechtenstein, Lithuania, Luxemburg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom.

*In countries marked with * a registration or renewal process is underway.*

Two formulations exist and are stored at different temperatures:

- Frozen formulation (stored at minus 15˚C) is approved 7 countries (Australia, US, Hong-Kong, Macau, Singapore, Canada and Israel)
- Refrigerated formulation (stored between 4-8˚C) in all countries including the above-listed with frozen formulation registered, except Israel. The refrigerated formulation is the one registered in Europe.

Discussion

No comments.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

[A0021]: What is the reimbursement status of the technology?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☒
- Other: use also Table 2 to document

Critical appraisal criteria Official documents on reimbursement processes and reliable data were considered.
A search through the websites of the main Medicines Agencies, HTA Agencies and Insurance Institutions was conducted and when the information were lacking the agencies were contacted by email.

The following websites were searched:

- AIFA (Italian Medicines Agency)
- AHTAPol (Agency for Health Technology Assessment in Poland)
- PBAC (Australian Government, Department of Health and Ageing, Pharmaceutical Benefit Advisory Committee)
- HAS (Haute Autoritè de Santè)
- INFARMED (National Authority of Medicines and Health Products in Portugal)
- KELA (Finland)
- NICE (National Institute for Health and Care Excellence)
- NOMA (The Norwegian Medicines Agency)
- SMC (Scottish Medicine Consortium) SULK (State Institute for Drug Control in Czech Republic)
- TLV (The Dental and Pharmaceutical Benefits Agency in Sweden)
- Health Canada.

Method of synthesis A descriptive system were performed.

Result

Current reimbursement status of zostavax for respective countries is presented in the table below.

Country	Reimbursed	Not reimbursed
Australia	Process on-going	
Austria		X
Belgium	Process on-going	
Canada	Process on-going	
Czech Republic		X
Denmark	no info	

Country	Reimbursed	Not reimbursed
England and Wales	X	
Finland	no info	
France		X
Germany		X
Greece		X
Italy		X
Norway		X
Poland		X
Portugal	?	
Scotland		X
Slovakia	no info	
Spain		X
Sweden	X	
The Netherlands	Process on-going	
USA (VA Pharmacy Benefits Management Services)	X	

To date (June 2013), ten countries recommend and/or fund zoster vaccination with ZOSTAVAX worldwide.

Country	Recommended	Funded/Reimbursed	Covered population (age om
Austria	Yes	No	50+
Germany	Yes – in Saxony Region	No	50+
Greece	Yes	No	60+
Sweden	No	Yes	50+
UK	Yes	Yes	70-79
Australia	Yes	Process on-going	61-79
Canada	Yes	Process on-going	60+
US	Yes	Yes	60+
Israel	Yes	No	60+
Korea	Yes	No	60+

US

HZ vaccine is recommended in individuals ≥60 year-olds. According to SPMSD, ZOSTAVAX is funded for a large part (more than 80%) of US citizens, either by public programmes (i.e. Medicare for 65+, Medicaid for low income, federal- and state-funded programs) or by private health insurances (commercial), providing full or partial reimbursement of the one-dose vaccine.

Australia

Zoster virus vaccine was originally registered by the TGA on 11 May 2006 as frozen formulation that must be stored below minus 15° C. A refrigerated formulation which can be stored between 2° and 8° C was registered on 19 June 2007.

PBAC decided to exclude the older population aged 80 and more for reimbursement. The reasons are: uncertain and high cost-effectiveness in this age group, very limited efficacy and safety data.

In the 60 to 79 year-olds, the vaccine cost-effectiveness has been recognised as mainly related to improvement in quality of life rather than on extension in life [PBCA 2008]. Initial uncertainties raised in 2007 were addressed (i.e. availability of a refrigerated formulation and no concomitant use with pneumococcal polysaccharide vaccine).

Canada

The National Advisory Committee on Immunization (NACI) recommends the use of ZOSTAVAX for the prevention of HZ and its complications in persons 60 years and older without contraindications [National Advisory Committee on Immunization 2010]. NACI indicated that ZOSTAVAX may be used in people aged 50 and older [Public Health Agency of Canada 2013].

To date there are no publicly-funded HZ vaccine programs in any province or territory in Canada. Canadians who are eligible for HZ vaccine may purchase Zostavax privately and private insurance plans may offer reimbursement.

Zostavax is not included in the formularies of provincial/territorial drug benefit programs, including the Ontario Drug Benefit (ODB) for those who have reached 65 years of age [Provincial Infectious Diseases Advisory Committee 2013].

Israel, Korea
Ministries of Health of Israel [Ministry of Health Israel 2013] and Korea [Korean CDC 2013] decided to recommend zoster vaccination in the population aged 60 and more. No decision has been taken so far on funding.

Sweden
In Europe, the first country which took a decision for reimbursement for ZOSTAVAX was Sweden. The Dental and Pharmaceutical Benefits Agency (TLV) granted reimbursement by inclusion of Zostavax in the pharmaceutical reimbursement scheme in May 2011 [Dental and Pharmaceutical Benefit Agency TLV 2011] with the condition to provide results of the 10 year follow-up of Zostavax (LTPS) with regards to the magnitude and duration of the protective effect.

Reimbursement is eligible for the population within the approved indication, i.e. individuals ≥ 50 year-olds. This decision was based on the following arguments:

- no alternative for HZ prevention;
- reasonable cost of vaccination from medical, humanitarian and socioeconomic aspects;
- proven efficacy in decreasing disease burden;
- cost-effective under many scenario handling uncertainties (incl. uncertain duration of protection).

UK
Early 2008, the UK Joint Committee on Vaccination and Immunisation (JCVI) has created a specific subgroup on the topic over the past years which gave a positive advice in March 2009 in favour of introducing HZ vaccination to people aged 70 and over, mainly driven by:

- the burden of illness and disease severity being greater in this age group
- the duration of protection (i.e. 7.5 years) at time of assessment, with the objective not to vaccinate too early to make sure people 70+ (the ones who will benefit the most) are protected
- decision supported by favourable economic profile.

Based on the work of the JCVI, UK Department of Health announced end January 2010 a universal HZ vaccination programme for adults aged 70-79 years should be introduced, provided that a vaccine is available at a cost-effective price [Joint committee on vaccination and immunisation 2010].

Early 2013, the UK department of health officialised the inclusion of ZOSTAVAX in the National Immunisation Programme (NIP) [UK Department of Health 2013]. As a consequence, the recommended population aged 70 to 79 will benefit from the vaccine free-of-charge under the National Health Service (NHS) setting. Exact implementation modalities will be announced later in 2013.

Austria
From 1st of January 2007, Austria is the first and only country in Europe to recommend HZ vaccination in all people first aged ≥60 years, and since the change in the European labelling, in population aged ≥50 years [Bundesministerium für Gesundheit 2013]. However, Zostavax is currently not on market in Austria. For that reason at the moment there is no recommendation on its use.

Germany
In 2010, a region from Germany, Saxony, has decided a zoster recommendation within the approved indication from 50 years of age [Sächsische Impfkommission 2010]. This is based on the assessment performed by the regional immunisation technical advisory group (SIKO). Germany plans to include herpes zoster vaccination into national immunization schedule [Stefanoff 2010].

Greece
In 2012, zoster vaccination has been added to the Greek vaccination plan for the population aged 60 and more [Ministry of Health Greece 2012]. The plan mentions that higher priority should be given to certain high risk groups only (including individuals with immunosuppression, asplenia, some chronic diseases, healthcare personnel). It is the first time that a vaccination is recommended and considered as 'not necessary' for all.

France

No recommendation concerning Zostavax has been given. The product is not reimbursed in France for the moment and the company has not applied for it yet France does not consider inclusion of herpes zoster vaccination among elderly into national immunization schedule because data on effectiveness herpes zoster vaccination among elderly were insufficient [Stefanoff 2010] at time of evaluation (2006).

Italy

Zostavax was evaluated by the Committee Prices and Reimbursement (CPR). The final decision taken in 2010 (Determinazione AIFA 16.04.10) [AIFA 2010] was not to reimburse HZ vaccine. It is included in class C as non-reimbursable medicine for which a prescription is required. At this moment, Zostavax is also not marketed in Italy.

Other countries

In some other European countries, health technology assessments of zoster vaccination have started and decisions of recommendation and/or funding of HZ vaccination can be expected in 2013 or later. HTA assessments on Zostavax are expected in the Netherlands (CVZ), Belgium (KCE) and Portugal (Infarmed). In the Czech Republic the vaccine is neither reimbursed nor presented on the market. In Malta, Zostavax is available but not reimbursed.

Discussion

The decision on the reimbursement of the HZ vaccine is decided at country level, Some differences are observed according to the healthcare system of the country in Europe. At national level the options are for:

- a programmatic approach with the inclusion of the HZ vaccination in the National Immunisation Programme (NIP), publicly funded and organised after a full assessment performed by a national committee
- the inclusion of HZ vaccine in the reimbursement scheme
- no reimbursement for Zostavax.

These approached can also be mixed at country level (e.g. some cohorts in NIP and others via a reimbursement scheme). Currently, the discussion on reimbursement of the HZ vaccine is reinitiated because the increased availability of the vaccine and new efforts from the MAH to retrieve reimbursement.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY

[B0001]: What is the technology and the comparator(s)?

What is the technology and the comparator(s)?
What is the mechanism of action of the technology?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☒
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

Zostavax is a lyophilized preparation of live, attenuated varicella-zoster virus (Oka/Merck strain), containing the same strain as in the vaccine against VZV-primo-infection (chickenpox). It is intended to be used in VZV-seropositive immunocompetent adults ≥50 years old,. To administer Zostavax, there is no need to check on the VZV status in terms of VZV seropositivity, history of HZ or prior vaccination with Zostavax. Zostavax is manufactured at a higher virus titre (14-fold higher potency) than varicella vaccine.

Zostavax® is a vaccine that is available as a powder and solvent to be made up into a suspension for injection. To reconstitute the vaccine, the solvent is inject in the pre-filled syringe into the vial of lyophilized vaccine. After reconstitution, 1 dose (0.65 ml) contains a minimum of 19,400 PFU (plaque forming units) [EMA 2013]. It is injected subcutaneously in the deltoid region of the upper arm.

Two formulations, stored at different temperatures, are available on the market:

- Frozen formulation (stored at minus 15°C) is approved 7 countries (Australia, US, Hong-Kong, Macau, Singapore, Canada and Israel);
- Refrigerated formulation (stored between 4-8°C), the present one registered in Europe. After reconstitution, it must be use immediately or within 30 minutes if stored at 20°C-25°C [EMA 2013].

In the Shingles Prevention Study [Oxman 2005] the estimated potency at vaccination of the 12 vaccine lots used in the study ranged from 18,700 to 60,000 plaque-forming units per dose. The median estimated potency of the zoster vaccine at vaccination was 24,600 PFU and more than the 90% of vaccinated persons received doses lower than 32,300 PFU.

The initial market authorization was granted for the frozen formulation. In the next procedure, EMA approved the refrigerated formulation of Zostavax, this while the pivotal clinical trials are based on the frozen formulation. Changes in formulation are justified by producer with the necessity to enable the use of Zostavax in expanded clinical settings

As requested by EMA in accordance to the guidelines on Clinical Evaluation of New Vaccines, comparative immunogenicity studies between both formulation have been conducted. In a bridging study [Gilderman 2008], the results of a RCT study comparing the safety and the immunogenicity of a refrigerator-stable formulation (44,846 PFU/0.65 ml) with those of the frozen formulation (56,845 PFU/0.65 ml) in persons >50 years of age are reported.

Each subject received a single (≈0.65 ml) subcutaneous injection of either the refrigerated (PGSU) or the frozen (PGS) formulation, each at a potency of approximately 50,000 PFU/dose. Immunocompetent participants (50 years of age and older) with a history of varicella or residence in a country where VZV infection is endemic were eligible for the study. 367 participants were vaccinated. The primary endpoints were the VZV antibody geometric mean titer (GMT; day 28), the VZV antibody geometric mean rise (GMR; days 1 to 28), and the incidence of vaccine-related serious adverse experiences (AEs) over 28 days.

The refrigerated (n=182) and frozen (n=185) formulations induced similar GMTs (727.4 and 834.4 gpELISA units/ml, respectively); the estimated GMT ratio (refrigerated formulation/frozen formulation) was 0.87 (95% confidence interval, 0.71 to 1.07). The GMRs were 2.6- and 2.9-fold, respectively. No vaccine-related serious AEs were reported in either group, and the safety profiles of the formulations were generally similar. In the bridging study, mortality and incidence of HZ or PHN have not been evaluated.

The conclusions of [Gilderman 2008] were criticized by [Levin 2009]. For [Levin 2009] comparable antibody titers on the basis of gpELISA results are not sufficient to claim a comparable immunogenicity. Authors of [Gilderman 2008] reply that VZV antibody titer measured by gpELISA at 6 weeks postvaccination correlated well with protection from HZ [Levin 2008]. Furthermore, they assured that the correlation between VZV antibody titer as determined by gpELISA and efficacy is presumed to be due to the fact that gpELISA measures T-cell-dependent antibody responses. Authors of [Gilderman 2008] welcomed investigations to advance understanding of VZV memory T-cell, effector T-cell, and antibody responses and protection against HZ.

Detailed information to investigate potential effects of dose potency and (duration of) freezing of the vaccine is not available [Bilcke 2012].

The comparator of zostavax is placebo because no other drug has been approved for the prevention of herpes zoster.

Mechanism of action (SmPC):

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.
Zostavax elicited both VZV antibody level as well as T-cell activity.

Discussion

Zostavax is compared with placebo. Indeed, because no other drug has been approved for the prevention of herpes zoster.

Approved potency and formulation differ from the ones studied in clinical trials. In the Shingles Prevention Study [Oxman 2005] the median estimated potency of the zoster vaccine at vaccination was 24,600 PFU and more than the 90% of vaccinated participants received doses lower than 32,300 PFU. While EMA requested that 1 dose (0.65 ml) contains a minimum of 19,400 PFU. No study investigated the possible dose-response relationship.

Nevertheless, EMA approved the refrigerated formulation of Zostavax even though the results of the clinical trials are based on the frozen formulation. The change in formulation was supported by a RCT trial [Gilderman 2008].. Although there seemed to be similar antibody titers measured on the basis of gpELISA, it has been questioned whether this antibody titer is a surrogate marker of threshold for immunity. The effectiveness of the refrigerated formulation has not been evaluated in a clinical trial for its effectiveness on mortality rates, prevention of HZ/PHN, long term safety etcetera. This means that follow-up data in daily practice are needed in order to assess whether the refrigerated formulation of the vaccine has a similar effectiveness and safety profile as the frozen formulation.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

[B0002]: What is the approved indication and the claimed benefit of the technology and the comparator(s)?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

According to summary of product characteristics [EMA 2013], Zostavax is indicated for prevention of herpes zoster and herpes zoster-related post-herpetic neuralgia (PHN). It is indicated for immunization of individuals 50 years of age or older.

According to the summary of product characteristics (package insert) approved by FDA [FDA 2013], Zostavax is a live attenuated virus vaccine indicated for prevention of herpes zoster (shingles) in individuals 50 years of age and older. It is not indicated for the treatment of PHN or prevention of variacella. No indication is made on prevention of PHN. In New Zealand, Zostavax is indicated for the prevention of HZ, prevention of PHN and reduction of acute and chronic zoster-associated pain.

Zostavax can be administered concomitantly with inactivated influenza vaccine as separate injections and at different body sites. Zostavax and a 23-valent pneumococcal polysaccharide vaccine should not be given at the same time because concomitant use in a clinical trial resulted in reduced immunogenicity of zostavax [EMA 2013].

Contraindications are:

- History of hypersensitivity to the active substance, to any of the excipients or trace residuals;
- 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;
- Active untreated tuberculosis;
- ZOSTAVAX should not be administered to pregnant women; furthermore, pregnancy should be avoided for for one month following vaccination [EMA 2013; CDCP 2008].

Discussion

ZOSTAVAX was developed for the prevention of herpes zoster and herpes zoster related post-herpetic neuralgia in individuals 50 years and older. EMA approved Zostavax for indicated for prevention of herpes zoster and herpes zoster-related post-herpetic neuralgia (PHN). While FDA approved it for prevention of herpes zoster only. In New Zealand, Zostavax is indicated for the prevention of HZ, prevention of PHN and reduction of acute and chronic zoster-associated pain. Apart from those authorization details, no other differences emerge at country level as far as indications of use of Zostavax are concerned.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

[B0003]: What is the phase of development and implementation of the technology and the comparator(s)?

Methods

Source of information:

- Basic documentation ☒

- Domain search ☒
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

Zostavax has already been approved by the EMA since 2006. The comparator in the clinical trials is placebo.

The production of HZ vaccine requires a complex manufacturing process which has led to limited supply capacities and restrictions in the amount of doses available for European countries, since its registration in 2006. Limited access was reported in Austria, Denmark, Finland, the Netherland, Norway, Sweden and Switzerland. In 2010 Zostavax was provided only to respond to specific and very limited requests from vaccination centres in Austria and the Netherlands. More recently, doses have been made available in limited quantities in the UK as part of the agreement that led to 2013 the first-ever national shingles immunisation campaign in Europe (See B0011 and A0023). The manufacturer of Zostavax (Merck Sharp & Dohme) declared to have plan for improvements of production processes and new manufacturing capacities. To increase production of the VZV-containing vaccines a new vaccine bulk manufacturing facility has been built in Durham, North California [Gerberding 2012].

Discussion

See A0020.

Real and long-term sustainable production capabilities for Zostavax represented a critical issue in the past. The manufacturer (Merck Sharp & Dohme) is making effort to facilitate the supply for all European countries in 2014.

References

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Importance and transferability

How important is this piece of information for decision making?
Critical ☒
Important ☐
Optional ☐
How transferable is this piece of information, i.e. can it be used in national decisions as such?
Completely ☒
Partly ☐
Not ☐

[B0004]: Who performs or administers the technology and the comparator(s)?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

The subcutaneous injectie of Zostavax will be administered by general practitioners (GP). According to the local regulations, nurses or pharmacists may be authorised to administer the HZ vaccine, under doctors' supervision. Because the limited availability of the vaccine, the most data are obtained from the USA.

In the USA Zostavax is recommended by the Advisory Committee on Immunization Practices (ACIP) to reduce the risk of shingles and its associated pain in people 60 years old or older. The vaccine is available in pharmacies and doctor's offices. The choice to get vaccinated is discussed by the doctor with patients.

In Europe, the administration of the vaccine may depend on whether a specific vaccination program will developed for this vaccine. In this case, Zostavax can be administered in a specialized vaccination centres where trained nurses are responsible for the administration of the vaccine. If there is no vaccination program, Zostavax will most likely be administrated by a GP.

Discussion

The subcutaneous injectie of Zostavax will be administered by a physician or a nurse. So it is likely to be utilized in the primary care via an outpatient setting. Where a vaccination program is approved, it could also be administered in vaccination centres. In the USA, Zostavax is recommended by the Advisory Committee on Immunization Practices (ACIP) and is available in pharmacies and doctor's offices.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

[B0005]: In what context and level of care is the technology and the comparator used?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

Zostavax is administered in the primary care but possibly in different ways, depending on the country. In some countries like the UK and USA, it is included in the national vaccination program while others opt for the inclusion of HZ vaccine in the reimbursement scheme (Sweden).

In A0011 and D0017, real life data on a HZ vaccination program conducted in the USA [Langan 2013] is reported. A cohort study of 766,330 fully eligible individuals aged >65 years was undertaken in a 5% random sample of Medicare. The individuals received either zoster vaccination or nothing between 1st January 2007 and 31st December 2009 [Langan 2013]. Of the eligible participants, 29,785 (3.9% of people; 2.1% of person-time) had HZ vaccination during the study period. Vaccination rates were lower in the oldest age group (1.5% in those aged 80 years or older). Overall, 154 vaccinees experienced incident herpes zoster episodes giving an incidence rate of herpes zoster in vaccinees of 5.4 (95% CI 4.6–6.4) per 1,000 person-years compared to 10.0 (95% CI 9.8–10.2) per 1,000 person-years in those not vaccinated [Langan 2013]. It is discussed that low vaccination degree of eligible individuals was caused by the limited availability of the vaccine and the problems with the use of the frozen version.

In [Tseng 2011], members of Kaiser Permanente Southern California (KPSC) at age 60 years or older, who received herpes zoster vaccine from 2007-2009 were studied. According to that retrospective cohort study 25% of patients was vaccinated. Individuals in the vaccinated cohort were more likely to be white, to be women, and to have had a larger number of outpatient visits and a lower prevalence of chronic diseases.

Discussion

See A0021, A0011 and D0017.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

[B0008]: What kind of special premises are needed to use the technology and the comparator(s)?

Methods

Source of information:

- Basic documentation ☐
- Domain search ☐
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

Zoster vaccination can be organized in different ways. The most prevailing ways to organise the administration of a vaccine is either via a national program (primary prevention) or via the gp/outpatient settings (on request of the recipient).

At national/local level the options for Zostavax reimbursement are for:

- a programmatic approach with the inclusion of the HZ vaccination in the National Immunisation Programme (NIP)
- an individualist approach with the inclusion of HZ vaccine in the reimbursement scheme
- no reimbursement of Zostavax.

In case of national/local programmatic approach for Zostavax, special premises could be necessary. The following points can be considered before implementation (not a limitative list):

- target population;
- vaccination center;
- personnel to involve;
- communication tools to contact and involve target population members;
- monitoring tools to assess coverage and efficacy of the vaccination programme;
- etc.

Zostavax is intended to be used in VZV-seropositive persons. However, there is no need for testing for VZV-seropositivity before its administration emerged.

Discussion

If Zostavax will be offered by a country, the necessity of special premises will depend on the chosen setting. (programmatic or individualistic approach for vaccination). There is no need for testing for VZV-seropositivity before its administration emerged.

References

No references.

Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

[B0009]: What supplies are needed to use the technology and the comparator?

Methods

Source of information:

- Basic documentation ☐
- Domain search ☐
- Other: [use also Table 2 to document]

Critical appraisal criteria

Method of synthesis

Result

There is no need of special supplies for a vaccination.

Discussion

References

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

[B0010]: What kind of data and records are needed to monitor the use of the technology and the comparator?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☐
- Other: [use also Table 2 to document]

Critical appraisal criteria Published EPAR

Method of synthesis Narrative

Result

With regards to use of ZOSTAVAX in Europe, SPMSD as the Marketing Authorisation Holder (MAH) has committed to implement Follow-Up Measures (FUM) decided at initial EMA application [EMA 2007].

Regarding the stability and calibration of varicella standards used for varicella potency assays,the applicant had committed to revise the procedure used for calibrating the varicella standard, to monitor the stability of the reference standards and to report the results on a regular basis. In conclusion, all quality issues are resolved [EMA 2007].

A Risk Management Plan (RMP) has been decided and further adapted to the expanded age group of individuals from 50 years of age and older [EMA 2007]. Long-term follow-up of vaccine efficacy (up to 10 years post-vaccination) has been conducted for a subgroup of participants ≥60 years included in the first phase III efficacy pivotal study (SPS). No similar follow-up was planned for the second phase III efficacy pivotal study (ZEST) where participants aged 50 to 59 were followed up to 2 years.

Long-term efficacy data were for the first time presented at ICAAC/IDSA 2008. Data from the SPS trial concerning vaccine efficacy for HZ cases and BOI by year after vaccination, were presented for up to 10 years. Estimates of vaccine efficacy against HZ as function of years after vaccination have been presented in [KCE 2010]. Estimates are available for the first 5 years after vaccination and are used in cost-effectiveness studies for the Belgium population. These are only estimates. No new clinical trials or clinical practice data are currently available.

Following specific EMA request, age-related ADRs analyses was performed on the data over the past 5 PSUR cycles (last 3 years) focusing on the elderly population i.e. aged 65 years and older.

EMA requested three studies:

- Post marketing, placebo-controlled general safety study;
- Large-scale (20 000 vaccinated participants) observational post licensure safety study;
- Clinical trial to assess long-term duration of protection among participants who received the vaccine during the efficacy trial.

SPMSD (MAH) presented the safety concerns together with the respective pharmacovigilance activities and proposed routine risk minimisation activities which are

regularly reviewed by the EMA. The latest RMP (v.6) was approved by the CHMP on 19 July 2012.Linked to Zostavax monitoring data there are surveillance programmes for HZ.

While in the USA the U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of the vaccine.

In Europe, not all countries have some form of surveillance for HZ [de Moira 2005] [Stefanoff 2010] [Statens Serum Institut 2010] and there is marked heterogeneity in the type of HZ surveillance systems that do exist (national mandatory or sentinel), the type of data collected (case-based or aggregated) and the reported case classification (clinical and/or laboratory).

Eleven countries (39%) developed surveillance system for herpes zoster. A national comprehensive surveillance systems exist in 6 countries (Czech Republic, Spain, Ireland, Malta, Slovakia, Slovenia) and sentinel in 5 countries (Belgium, France, Ireland, Netherlands, UK) [Stefanoff 2010].

Aggregated data on herpes zoster cases are collected in 3 countries (Spain, Ireland, UK). In 9 countries (Belgium, Czech Republic, France, Ireland, Germany, Malta, Netherlands, Slovakia, Slovenia) case-based data are collected [Stefanoff 2010].

Although these surveillance systems in the European countries are not specifically developed for the monitor of Zostavax, these monitoring systems can certainly be used to assess the effect of the vaccination on the incidence of HZ. It may be therefore recommended to use these monitoringsystems if a country decided to reimburse Zostavax for specific agegroups.

Discussion

EMA required follow-up measures for Zostavax. Furthermore, a Risk Management Plan (RMP) has been decided and further adapted to the expanded age group of individuals from 50 years of age and older.

Linked to Zostavax monitoring data there are surveillance programmes for HZ. Not all countries have some form of surveillance in place for HZ and, where present, such surveillance shows marked heterogeneity. National mandatory or sentinel systems could be present and data collected could be aggregated or be case-based. The surveillance systems may be used to assess the effect of the vaccination on the incidence of HZ.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

[B0011]: What kind of registry is needed to monitor the use of the technology and the comparator?

Methods

Source of information:

- Basic documentation ☒
- Domain search ☒
- Other: [use also Table 2 to document]

Critical appraisal criteria Not applicable

Method of synthesis Narrative

Result

At national/local level, decisions can be taken upon the implementation of vaccination programmes for all the population aged 50 years or older, or for specific subgroups. If a vaccination programme is adopted, data should be collected on:

- health status of the target population
- HZ vaccine coverage rates
- HZ vaccine effectiveness
- HZ vaccine adverse events.

Vaccination programmes involving Zostavax are under way in the USA. In the USA Zostavax is recommended by the Advisory Committee on Immunization Practices (ACIP) to reduce the risk of shingles and its associated pain in people 60 years old or older. In addition, Zostavax is also funded in a large part (more than 80% -internal data) of USA citizens, either by public programmes (i.e. Medicare for 65+, Medicaid for low income, federal- and state-funded programs) or by private health insurances (commercial), providing full or partial reimbursement of the one-dose vaccine. In USA, Zostavax is available in pharmacies and doctor's offices. Zostavax can be administered concurrently with all other live and inactivated vaccines, including those routinely recommended for persons in 60 years and older age group, such as influenza and pneumococcal vaccines. It should be noted that concurrent administration of Zostavax with pneumococcal vaccines is not in line with the restriction in the advice of the EMA.

At this moment, UK is preparing the launch of the first-ever national shingles immunisation campaign in Europe. Eligible senior members of the public will be able to receive the Zostavax vaccine during regular health visits or at the same time for their seasonal flu. The vaccination programme involve people aged 70, with a catch-up programme for those aged up to, and including, 79 years. The programme will begin in September 2013 and it is estimated that around 800,000 people in the UK will be eligible for the vaccine in the first year [Department of Health 2013]

According to the submission file, zoster vaccination is under evaluation in Greece. A Greek vaccination plan for the population aged 60 and more is under study. The plan mentions that higher priority should be given to certain high risk groups only (including those with immunosuppression, asplenia, some chronic diseases, or healthcare personnel).

Discussion

Collecting data on HZ vaccine effectiveness requires to define an adequate follow up period. That choice is linked to the duration of protection offered by HZ vaccine (for duration of protection, see D00011E). The monitoring and presence of a specific register

could partially be overlapping the traditional pharmacovigilance systems implemented at national level.

Vaccination programmes are under way or planned in the USA and UK.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

SAFETY

[C0001A]: What kind of harms can use of Zostavax cause to the patient?

[C0001B1]: What are the most frequently reported side effects?

What are the adverse events of Zostavax vaccination in persons ≥50 years? What is their type and frequency?

Methods

X See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation (REA submission file of SPMSD, SPC and EPAR's of Zostavax by CHMP/EMA) ☒
- Domain search ☒
- Other: [use also Table 2 to document]

Critical appraisal criteria: MedDRA Dictionary Terminology (as used in SPC) for body system organ class of adverse event, frequency and severity (CTCAE grades 3 and 4);

- 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

Method of synthesis: narrative.

Result

[EMA/CHMP, SPC of Zostavax (2006; last update 17/03/2013)]:

Data hereabout is based on an evaluation of several clinical trials, including the Shingles Prevention Study (SPS), with more than 40000 adults (older than 60 years), and the Zostavax Efficacy and Safety Trial (ZEST) with over 22000 adults (age 50-59 years old). Vaccine-related injection-site and systemic adverse reactions have been reported at a significantly greater incidence in the vaccine group versus the placebo group. Administration site conditions are very common (seen in more than 10% of the patients). Headache and pain in extremity are common (seen in 1-10% of the patients).

The below table of the SPC presents vaccine-related injection-site and systemic adverse reactions reported in the Adverse Event Monitoring Substudy of the SPS. It 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".

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 (≥1/100 to <1/10)
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 (≥1/100 to <1/10)

MedDRA System Organ Class	Adverse reactions	Frequency
General disorders and administration site conditions	Erythema †*, Pain/tenderness †*, Swelling†*, Pruritus† Haematoma†, Warmth†, Induration† Rash †, Urticaria †, Pyrexia	Very common (≥1/10) Common (≥1/100 to <1/10) Not known**
Infections and infestations	Varicella	Very rare (<1/10,000)

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

[EMA-EPAR variation (2006)]

Safety data for persons 50-59 years old.

Table. Statistical analysis of clinical adverse experiences based on data combined from protocol 010 and protocol 011 following administration of ZOSTAVAX (days 1 to 28 postvaccination).

	Age Group [years]				Risk Difference (95% CI)
	50-59 N=389		60 or more N=731		
	n	Risk	n	Risk	
One or more adverse experiences	231	60.3%	323	44.2%	16.1 (10.0; 22.1)
Injection-site adverse experiences	193	50.4%	250	34.2%	16.1 (10.0; 22.2)
Systemic adverse experiences	96	25.1%	139	19.0%	6.1 (1.0; 11.4)
Vaccine-related adverse experiences	199	51.9%	256	35.1%	16.9 (10.8; 22.9)
Injection-site adverse experiences	193	50.4%	249	34.1%	16.3 (10.2; 22.3)
Systemic adverse experiences	22	5.7%	21	2.9%	2.8 (0.4; 5.8)
Serious adverse experiences	1	0.3%	5	0.7%	-0.4 (-1.4; 0.9)
Serious vaccine-related adverse experiences	0	0.0%	0	0.0%	0.0 (-0.5; 1.0)
Death	0	0.0%	0	0.0%	N/A
Discontinuation due to an adverse experience	0	0.0%	1	0.1%	-0.1 (-0.8; 0.9)
Discontinuation due to a vaccine-related adverse experience	0	0.0%	0	0.0%	N/A
Discontinuation due to a serious adverse experience	0	0.0%	1	0.1%	-0.1 (-0.8; 0.9)
Discontinuation due to a serious adverse experience	0	0.0%	0	0.0%	N/A

Source: *Adapted from EMA. ZOSTAVAX®- EPAR - Product Information - Summary of Product Characteristics. 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000674/WC500053462.pdf*

As shown in the table above, 60.3% of participants 50-59 years of age reported one or more clinical adverse experiences, whereas 44.2% of participants ≥60 years of age reported one or more clinical adverse experiences. In participants 50-59 years of age, approximately 25.1% of participants reported systemic clinical adverse experiences, but only 5.8% of participants reported vaccine-related systemic clinical adverse experiences. In participants ≥60 years of age, 19.0% of participants reported systemic clinical adverse experiences, but only 2.9% of participants reported vaccine-related systemic clinical adverse experiences.

These results indicate overall a higher rate of adverse events in the lower age group.

The overall incidence of adverse experiences from the nervous system organ class (SOC) was statistically higher in the younger age group than in the older age group, with

headache reported at a significantly higher frequency by participants 50-59 years of age than by participants ≥60 years of age.

[FDA Leaflet. US SPC (2006; revised June 2011)]

The most frequent adverse reactions, reported in ≥1% of participants vaccinated with ZOSTAVAX, were headache and injection-site reactions.

The overall incidence of vaccine-related injection-site adverse reactions within 5 days post-vaccination was greater for participants vaccinated with ZOSTAVAX as compared to participants who received placebo (63.6% for ZOSTAVAX and 14.0% for placebo). Injection-site adverse reactions occurring at an incidence ≥1% within 5 days post-vaccination are shown in table 1.

Table. Injection-site adverse reactions reported in ≥1% of adults who received ZOSTAVAX or placebo within 5 days post-vaccination in the Zoster Efficacy and Safety Trial (participants 50-59 years old).

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

**Solicited on the Vaccination Report Card.*

Source: *Adapted from* FDA. ZOSTAVAX® Package insert. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM132831.pdf

Systemic adverse reactions and experiences reported during days 1-42 at an incidence of ≥1% in either vaccination group were headache (ZOSTAVAX 9.4%, placebo 8.2%) and pain in the extremity (ZOSTAVAX 1.3%, placebo 0.8%), respectively. The overall incidence of systemic adverse experiences reported during days 1-42 was higher for ZOSTAVAX (35.4%) than for placebo (33.5%).

Table. Injection-site adverse reactions* in ≥1% of adults who received ZOSTAVAX or placebo within 5 days postvaccination from the AE Monitoring Substudy of the Shingles Prevention Study (participants ≥ 60 years old).

Injection-Site Adverse Reaction	**ZOSTAVAX** (N =3345), in %	**Placebo** (N =3271), in %
*Solicited**		
Erythema	35.6	6.9
Pain/Tenderness	34.3	8.3
Swelling	26.1	4.5
Unsolicited		
Hematoma	1.6	1.4
Pruritis	6.9	1.0
Warmth	1.6	0.3

**Patients instructed to report adverse experiences on a Vaccination Report Card*
***Solicited on the Vaccination Report Card*
Source: *Adapted from* FDA. ZOSTAVAX® Package insert. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM132831.pdf

[Simberkoff (2010)]; (Adverse Event Monitoring Substudy of SPS; n= 6616; mean follow-up: 3.4 years):

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

[Schmader (2012)]; (Zoster Efficacy and Safety Trial; n=22396; participants 50-59 years; mean follow-up: 1.3 years).

The overall incidence of vaccine-related injection-site adverse experiences was significantly greater for participants vaccinated with ZOSTAVAX versus participants who received placebo (63.9% for ZOSTAVAX and 14.4% for placebo). Most of these adverse reactions were reported as mild in intensity.

[Gagliardi (2012; Cochrane review)]

Vaccine-related systemic adverse effects were more frequent in the vaccinated group (RR 1.29, 95% CI: 1.05 to 1.57, number needed to treat to harm (NNTH) = 100). The pooled data risk ratio for adverse effects for participants with one or more inoculation site adverse effect was RR 4.51 (95% CI: 2.35 to 8.68), and the NNTH was 2.8 (95% CI: 2.3 to 3.4). Side effects were more frequent in younger (60 to 69 years) than in older (70 years and over) participants.

[Kerzner (2007)]

Concomitant administration of Zostavax and **inactivated Influenza vaccine** (three vaccine strains; 2005–2006 influenza season) in adults ≥50 years (n=762): No serious AEs related to ZOSTAVAX were observed during the study.

CONCLUSION of Kerzner: ZOSTAVAX and influenza vaccine given concomitantly are generally well tolerated in adults aged 50 and older.

[MacIntyre (2010)]

Concomitant administration with **pneumococcal vaccines (PP V23)** in adults ≥60 years (n=473): Four weeks postvaccination with ZV, clinical AEs were numerically but not significantly higher in nonconcomitant group. The incidence of injection-site AEs was similar in both groups. All 6 reported serious AEs were deemed not related to study vaccine.

CONCLUSION of McIntyre: When administered concomitantly, ZV & PP V23 were generally well tolerated.

[EMA SPC Zostavax (2006)]

- The safety of ZOSTAVAX have not been established in adults who are known to be **infected with HIV** with or without evidence of immunosuppression. immunosuppression due to HIV/AIDS is denominated as a contraindication. A clinical trial (NCT00851786) for further investigation is ongoing.
- In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX was administered to 206 participants 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.
- Based on limited data from 2 clinical trials (Macaladad 2007, Diaz 2006) that enrolled **VZV-seronegative** or low seropositive participants (27 participants 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 participants who received ZOSTAVAX in clinical trials, with 2 of the 27 participants reporting fever. No participants reported varicella-like or herpes zoster-like rashes. No serious vaccine-related adverse experiences were reported.

[Gilderman 2008]

Immunogenicity study of a refrigerator-stable formulation of Zostavax; n=368; participants ≥ 50 years; follow-up: 28 days.

Clinical AEs were reported at a lower rate by the recipients of the Zostavax refrigerated formulation than by the recipients of the Zostavax frozen formulation. The most frequently reported injection-site AEs (10% in both vaccination groups) were erythema, pain, and swelling. The incidences of systemic clinical AEs were similar in both vaccination groups, with 6% determined to be vaccine related in either vaccination group. One non-injection-site varicella-like rash with three lesions was reported by one subject in the Zostavax (refrigerated form) group. No subject discontinued the study due to an AE.

[Mills 2010]
Safety, tolerability, and immunogenicity of zoster vaccine in persons with a history of HZ; n=101; participants ≥50 years of age, follow up: 28-days.No serious AEs were reported within the 28-day safety follow-up period. The proportion of participants reporting systemic AEs was similar in both arms. Two vaccine-related systemic AEs were reported in participants following administration of zoster vaccine: pain and myalgia of moderate intensity; and axillary pain of mild intensity. The rate of reported injection-site AEs was higher in vaccine recipients (45.9%) than in placebo recipients (4.2%). One varicelliform rash was noted in both the HZ vaccine group and the placebo group. The most frequently reported injection-site AEs in vaccine recipients were erythema (33.7%), pain (36.7%) and swelling (26.5%).

Discussion

In the clinical studies, the overall incidence of vaccine-related injection-site adverse reactions was significantly greater for participants vaccinated with ZOSTAVAX (frozen formulation) versus participants who received placebo (48% versus 17% in SPS Substudy and 63.9% versus 14.4% in the ZEST; data FDA). Vaccine-related systemic adverse effects were more frequent in the vaccinated group (RR 1.29, 95% CI: 1.05 to 1.57, number needed to treat to harm (NNTH) = 100).

The most common side effects with Zostavax are reactions at the site of the injection (redness, pain, swelling, itching, warmth and bruising).

The number and percentage of participants reporting any systemic clinical adverse experience were greater in the 50 to 59 year group (ZEST) as compared to the ≥ 60 year group (SPS). Within the SPS, side effects were more frequent in younger (60 to 69 years) than in older (70 years and over) participants.

The safety of Zostavax in HIV infected adults has not been established. Concomitant administration of Zostavax with influenza vaccine, pneumococcal vaccine and systemic corticosteroids (at a daily equivalent of 5 to 20 mg of prednisone) were generally well tolerated.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

[C0001B2]: What are the severe side effects (grade 3 or 4 according to Common Terminology Criteria)?

Methods

☐ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation (REA submission file of SPMSD, SPC and EPAR's of Zostavax by CHMP/EMA) ☒
- Domain search ☒
- Other: [use also Table 2 to document]

Critical appraisal criteria: MedDRA Dictionary Terminology (as used in SPC e.g.) for body system organ class of adverse event, frequency and severity (grades 3 and 4);

- 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

Method of synthesis: narrative and trend analysis (linear regression with constant whose unstandardized predicted values are reported).

Result

[FDA Leaflet (2006)]

Table. Number of participants with ≥1 serious adverse events (0-42 days postvaccination) in the Shingles Prevention Study (adjusted by adding risk difference).

cohort	**ZOSTAVAX** n/N (%)	**Placebo** n/N (%)	**Risk Difference (%)**	**Relative Risk (95% CI)**
Overall Study Cohort: ≥60 years)	255/18671 (1.4)	254/18717 (1.4)	0	1.01 (0.85, 1.20)
Subgroups:				
60-69 years	113/10100 (1.1)	101/10095 (1.0)	0.1	1.12 (0.86, 1.46)
70-79 years	115/7351 (1.6)	132/7333 (1.8)	-0.2	0.87 (0.68, 1.11)
≥80 years	27/1220 (2.2)	21/1289 (1.6)	0.6	1.36 (0.78, 2.37)
AE Monitoring Substudy Cohort (≥60 years old)	64/3326 (1.9)	41/3249 (1.3)	0.6	1.53 (1.04, 2.25)
Subgroups:				
60-69 years	22/1726 (1.3)	18/1709 (1.1)	0.2	1.21 (0.66, 2.23)
70-79 years	31/1383 (2.2)	19/1367 (1.4)	0.8	1.61 (0.92, 2.82)
≥80 years	11/217 (5.1)	4/173 (2.3)	2.8	2.19 (0.75, 6.45)

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

Source: *Adapted from* FDA. ZOSTAVAX® Package insert. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM132831.pdf

[Fried (2010)]:

A subset of SPS participants monitored closely for serious adverse events (SAEs) in the first 6 weeks after vaccination had a greater risk of SAEs with older age.

There were 53% more SAEs overall (P=0.04) with vaccine than with placebo, but only 21% more in persons aged 60 to 69 (P=0.53), 61% more in persons aged 70 to 79 (P=0.12), and 219% more in persons aged 80 and older (P=0.19). When the two older groups were combined, there were 75% more SAEs in participants aged 70 and older with vaccine (P=0.03).

[EMA/CHMP, Scientific discussion (EPAR) of Zostavax (2006)]:

Serious Adverse Event (SAE)

In protocol 004 (SPS) routine safety monitoring cohort (days 0 to 42 post vaccination) including all participants, the percentage of participants with one or more systemic adverse events was 1.37 % in the zoster group and 1.36% in the placebo group. Only 5 serious adverse events (within 42 days after vaccination) were assessed by the investigators as at least possible vaccine-related; two were in the zoster vaccine group:

- A 80 year old man developed joint pain, swelling, and stiffness on day 3 post vaccination. He was later diagnosed with polymyalgia rheumatica.
- A 64 year old woman with a history of asthma experienced an exacerbation of asthma on day 2 post vaccination.

Within the three placebo cases, there was one case of an anaphylactic reaction 90 minutes after administration of placebo. Information is insufficient to assess whether the AE was related to a pre-existing peanut allergy or caused by hydrolyzed porcine gelatine (used as a stabilizer and present in the placebo formulation).

The rates of HZ-related hospitalisation in the zoster vaccine group (5 hospitalisations) and the placebo group (6 hospitalisations) were not different.

In protocol 007 and 009, a total of 10 participants reported SAEs but none was determined by the investigator to be vaccine related.

[EMA-CHMP EPAR variation (2006)]

Table. Statistical Analysis of Clinical Adverse Experiences Based on Data Combined from Protocol 010 and Protocol 011 Following Administration of ZOSTAVAX (Days 1 to 28 Postvaccination).

	Age group				Estimated Risk Difference in Percentage Points (95% CI)
	50-59 years (N=389)		≥60 years (N=731)		
	n	Estimated risk (%)	n	Estimated risk (%)	
Number of subjects vaccinated	389		731		
Subjects with follow-up	382		730		
Number (%) of subjects vaccinated:					
- with one or more adverse experiences	231	(60.3)	323	(44.2)	16.1 (10.0, 22.1)
- with serious adverse experiences	1	(0.3)	5	(0.7)	-0.4 (-1.4, 0.9)

N = Number of subjects vaccinated.
n = Number of subjects reporting adverse experiences in the respective category.

Source: *Adapted from* EMA. ZOSTAVAX®- EPAR - Product Information - Summary of Product Characteristics. 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000674/WC500053462.pdf

One (0.3%) out of 382 participants with safety follow-up and 5 (0.7%) out of 730 participants with safety follow-up reported serious clinical adverse experiences in the age group of 50-59 years and the age group of >60 years respectively. These events were convulsion, gastroenteritis, basal cell carcinoma, cardiac failure congestive, aortic valve stenosis, arrhythmia, myocardial infarction, acute pulmonary edema, chronic obstructive pulmonary disease, pneumonia, respiratory failure and upper limb fracture. No ZOSTAVAX related serious clinical adverse experience was reported in the two studies. Furthermore, no deaths occurred during the conduct of either study.

[Oxman (2005)] SPS (Shingles Prevention Study; n=38546; participants >60 years, f-up: 42 days) and EMA/CHMP:

- Vaccine-related serious adverse reactions is observed in 2 participants in the Zostavax group (asthma exacerbation and polymyalgia rheumatica) and in 3 participants in the placebo group (Goodpasture's syndrome, anaphylactic reaction and polymyalgia rheumatica).

[Schmader/Levin (2012)] ZEST: Efficacy and Safety Trial; n=22396; participants 50-59 years; mean follow-up: 1.3 years.

- AEs were reported by 72.8% of participants in the ZV group and 41.5% in the placebo group, with the difference primarily due to higher rates of injection-site AEs and headache.
- The proportion of participants reporting SAEs occurring within 42 days postvaccination (ZV: 0.6%; placebo: 0.5%) (relative risk 1.13; 95% CI: 0.81–1.60) and 182 days postvaccination (ZV: 2.1%; placebo: 1.9%) (relative risk: 1.11; 95% CI: 0.92–1.33) was similar between groups.
- A vaccine-related serious adverse experience was reported in 1 subject vaccinated with ZOSTAVAX (anaphylactic reaction).

[Schmader (2012)] ZEST

Table. Clinical Adverse Experience Summary (days 1-42 postvaccination)

	Zostavax N=11 094		Placebo N=11 116		Risk Difference (95% CI)
	n	Risk	n	Risk	
Subjects vaccinated and safety follow-up	11094		11116		
One or more adverse experiences	8080	72.8%	4613	41.5%	31.3 (30.1; 32.6)
-Injection-site adverse experiences	7089	63.9%	1596	14.4%	49.5 (48.4; 50.6)
-Systemic adverse experiences	3932	35.4%	3722	33.5%	2.0 (0.7; 3.2)
Vaccine-related adverse	7213	65.0%	1988	17.9%	47.1 (46.0;

	Zostavax N=11 094		Placebo N=11 116		Risk Difference (95% CI)
	n	Risk	n	Risk	
experiences					48.3)
-Injection-site adverse experiences	7089	63.9%	1596	14.4%	49.5 (48.4; 50.0)
-Systemic adverse experiences	746	6.7%	526	4.7%	2.0 (1.4; 2.6)
Serious adverse experiences	69	0.6%	61	0.5%	0.1 (-0.1; 0.3)
-Serious vaccine-related adverse experiences	1	0.0%	0	0.0%	0.0 (0.0; 0.1)
-Death	1	0.0%	3	0.0%	0.0 (0.0; 0.0)

Source: *Adapted from Schmader KE, Levin MJ, Gnann JW Jr, et al. Efficacy, Safety, and Tolerability of Herpes Zoster Vaccine in Persons Aged 50-59 Years. Clin Infect Dis 2012;54(7):922-8.*

[Tseng (2012)]

The aim of the Vaccine Datalink Study was to examine a large cohort of adults who received the zoster vaccine for evidence of an increased risk of *prespecified* adverse events requiring medical attention. A total of 193,083 adults aged 50 and older receiving a zoster vaccine from 1 January 2007 to 31 December 2008 were included.

The risk of allergic reaction[11] was significantly increased within 1–7 days of vaccination (relative risk = 2.13, 95% confidence interval (CI): 1.87–2.40 by case-centred method and relative rate = 2.32, 95% CI: 1.85–2.91 by self-controlled case series). No increased risk was found for the following adverse event groupings: cerebrovascular events, cardiovascular events, meningitis; encephalitis, encephalopathy, Ramsay-Hunt syndrome and Bell's palsy.

The medical records of patients who were reported as having an allergic reaction (n=118) were objected to a further review. Of the 71 patients whose medical visit was determined to be the result of a reaction to the zoster vaccine, most (n=59, 83%) complained of a localized inflammatory response with varying degrees and combinations of redness, swelling and/or tenderness at the site of the injection. Eleven (15%) presumably allergic, pruritic, urticarial, macular or papular rashes were described. A single patient was described as having a zosteriform rash a few hours after getting the shingles vaccine.

[Vermeulen (2012)]

A randomized, double-blind, multicenter study with 210 participants ≥60 years old compared immunity and safety profiles after one and two doses of ZV, separated by 6 weeks, versus placebo. Adverse experiences (AEs) were recorded on a standardized Vaccination Report Card. Results: No serious vaccine-related AEs occurred.

Table. Adverse experience summary (Days 0–42 postvaccination).

	Zoster vaccin		Placebo	
	n	(%)	n	(%)
Number of subjects	104		105	
With one or more AE	74	(71.2)	46	(43.8)
With serious AEs	0	(0)	0	(0)

Source: *Adapted from Vermeulen JN, Lange JMA, Tyring SK, et al. Safety, tolerability, and immunogenicity after 1 and 2 doses of zoster vaccine in healthy adults >60 years of age. Vaccine 2012;30:904-10.*

[11] Allergic reactions include the next ICD-9 codes:
995.1 Angioneurotic oedema
995.2 Adverse effects of drug
995.3 Allergy unspecified
708.0 Allergic urticaria
708.1 Idiopathic urticaria
708.9 Urticaria, unspecified
999.5 Serum reaction
995.0;999.4 Anaphylaxis

[SPMSD submission file (2013)]:

Information in the following table is provided by the marketing authorisation holder (MAH) of Zostavax.

Table. Reports and events in patients 65 to 74 years, 75 to 84 years, and >85 years of age identified 02-May-2012 to 01-Nov-2012.

Age group [years]	Reports in total	Reports on serious AE		Events in total	Serious events	
	N	n	%	N	n	%
65-74	306	23	8	761	56	7
75-85	181	12	7	403	34	8
Older than 85	31	5	16	59	14	24

Source: *Adapted from Sanofi Pasteur MSD France. Marketing Authorization Holder submission file for shingles (herpes zoster) vaccine (live) Zostavax®. Submission date 12-04-2013.*

According to SPMSD, the definition of serious adverse events corresponding to the regulatory definition is as followed:

An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect [DIR 2001/83/EC Art 1(12)].

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

The use of this term, however, does not imply, necessarily, that the reported events occurred due to an effect of the product either in the opinion of the MAH, or in the opinion of the reporter, or in fact.

According to the unpublished information of SPMSD, higher age is correlated to a higher incidence of serious adverse event within the group of 65 years and older.

[Oxman (2005)]

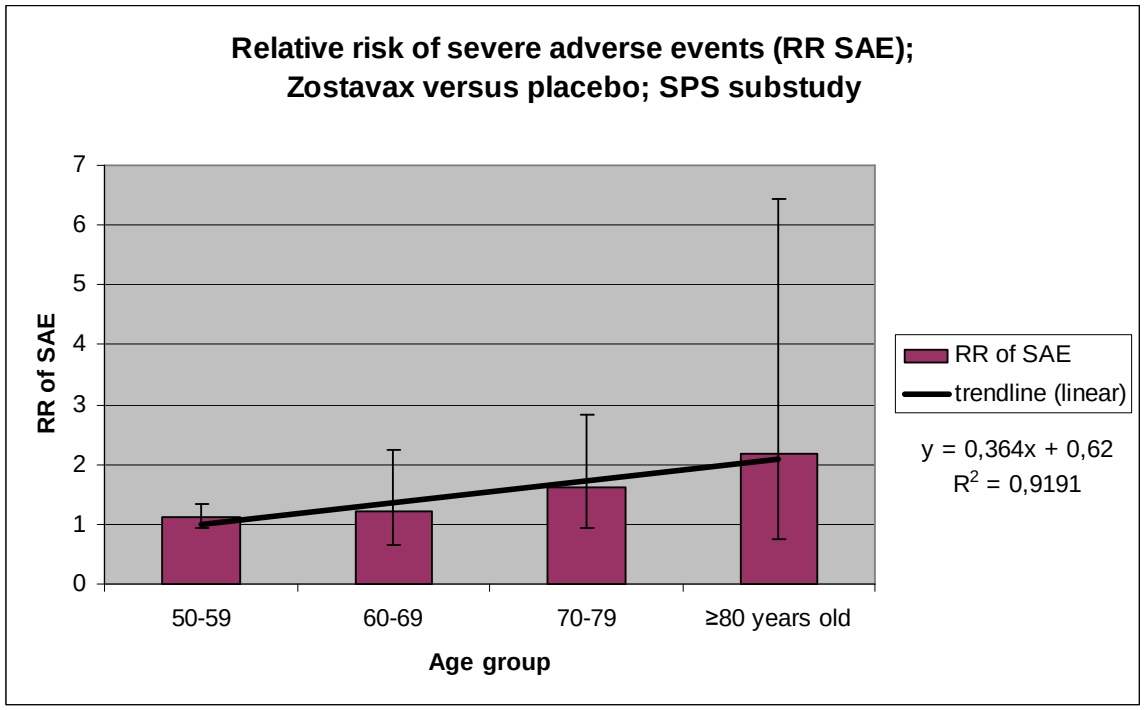
Serious Adverse Events:

A serious adverse event was one which:

1. Resulted in death; or
2. Was life-threatening (any adverse event that, in the opinion of the investigator or the initial reporter, placed the subject at immediate risk of death from the adverse event as it occurred) [Note: This does not include an adverse event that, had it occurred in a more serious form, might have caused death.]; or
3. Resulted in persistent or significant disability or incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions); or
4. Resulted in or prolonged an existing in-patient hospitalisation (i.e., an overnight stay in the hospital, regardless of length of stay, even if the hospitalisation was a precautionary measure for continued observation) [Note: Hospitalisation for surgery (or an elective hospitalisation) for a pre-existing condition which had not worsened did not constitute a serious adverse event.]; or
5. Was a cancer; or
6. Was the result of an overdose (whether accidental or intentional); or
7. Was another important medical event that may not result in death, not be life-

threatening, or not require hospitalisation that was considered to be a serious adverse event when, based upon appropriate medical judgment, the event might have jeopardized the subject and might require medical or surgical intervention to prevent one of the outcomes listed above.

Trend analysis: Age dependency of the outcome SAE.



Data from Schmader (age group 50-59) and FDA (other age groups). A good relation between age and relative risk of serious adverse event due to Zostavax can be seen (R^2 = 0,9191; R^2-adj: 0.879). Vaccination with Zostavax leads to an age-dependent enlarged chance for SAE.

Discussion

After zoster vaccination, the risk of serious adverse events (SAEs) are slightly enhanced after Zostavax administration (frozen formulation) as compared to the placebo group in the total cohort of participants 60 years of age and older. The relative risk is 1.01 (95% CI: 0.85-1.20) for the overall study of SPS (N=37388) and 1.53 (95% CI: 1.04-2.25) for the Adverse Events Monitoring Substudy (N=6575). In the Substudy, there were overall 53% more SAEs (P=0.04) with vaccine than with placebo.

AE in participants of 50-59 years old is studied in the ZEST (N=22439). The proportion of participants reporting SAEs occurring within the 42-days period postvaccination was similar in the Zostavax (0.6%) and placebo (0.5%) groups (relative risk, 1.13; 95% CI: 0.81-1.60).

Reported SAE's were: convulsion, gastroenteritis, basal cell carcinoma, cardiac failure congestive, aortic valve stenosis, arrhythmia, myocardial infarction, acute pulmonary oedema, chronic obstructive pulmonary disease, pneumonia, respiratory failure and upper limb fracture. Also polymyalgia rheumatica, exacerbation of asthma, anaphylactic reaction and Goodpasture's syndrome have been reported.

Age is a risk factor for SAE's. In both study arms, the number of participants with ≥1 serious adverse events increases with age. This increase is even more in the Zostavax group. In the SPS substudy, the group of ≥80 years had twice the chance to get a SAE (relative risk 2.19; 95% CI: 0.75-6.45; P=0.19) after vaccination as compared to placebo. Participants aged 60-69 years old had 21% more risk (P=0.53) and participants aged 70-79 years old had 61% more risk (P=0.12).

When the two older groups were combined, there were 75% more SAEs in participants aged 70 and older after vaccination with Zostavax (P=0.03).

The increased risk on SAEs by age and by Zostavax is confirmed by recent safety information provided by the MAH. This relation was confirmed by the trend analysis of the relative risks of SAE between individuals vaccinated with Zostavax versus the placebo group seen (R^2 = 0,9191; R^2 -adj: 0.879). Vaccination with Zostavax leads to an age-dependent enlarged chance for SAE.

In 1-7 days after administration of the vaccine there is a small, but significantly increased risk of allergic reactions which require medical attention (relative risk = 2.13, 95% CI: 1.87-2.40 by case-centred method and relative rate = 2.32, 95% CI: 1.85-2.91 by self-controlled case series). Age specific information about allergic reaction is not available. Among those cases, more than 80% of the events involved localized inflammatory response with various degrees and combinations of redness, swelling and/or tenderness at the site of the injection.

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1. European Medicine Agency. European Public Assessment Report (EPAR) Zostavax®. London, 19/05/2006. Scientific discussion. Available at URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000674/WC500053460.pdf
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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒ (subgroup analyses)
Not ☐

[C0004]: How will the long-term safety be studied/ monitored?

Methods

☐ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation (REA submission file of SPMSD, SPC and EPAR's of Zostavax by CHMP/EMA) ☒
- Domain search ☐
- Other: ☒ [use also Table 2 to document]: including documents of the Federal Drug Administration (FDA) of the United States.

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: narrative.

Result

[SPMSD submission file (2013)]

Long-term follow-up of vaccine efficacy (up to 10 years post-vaccination) has been conducted for a subgroup of participants ≥60 years included in the first phase III efficacy pivotal study (SPS). No similar follow-up was planned for the second phase III efficacy pivotal study (ZEST) where participants aged 50 to 59 were followed up to 2 years.

The safety profile of ZOSTAVAX has been closely monitored since the introduction of this vaccine on the market. Its safety profile is under regular review and the label is updated as new adverse reactions are identified Periodic Safety Update Report (PSUR).

Following specific EMA request, age-related ADRs analyses was performed on the data over the past 5 PSUR cycles (last 3 years) focusing on the elderly population i.e. aged 65 years and older. A review of reports was done for the following age-groups: 65-74 years, 75-85 years and >85 years. As an example:

Table. Reports and events in patients 65 to 74 years, 75 to 84 years, and >85 years of age identified 02-May-2012 to 01-Nov-2012.

Age group [years]	Reports in total	Reports on serious AE		Events in total	Serious events	
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75-85	181	12	7	403	34	8
Older than 85	31	5	16	59	14	24

Source: *Adapted from Sanofi Pasteur MSD France. Marketing Authorization Holder submission file for shingles (herpes zoster) vaccine (live) Zostavax®. Submission date 12-04-2013.*

[SPMSD submission file (2013)]

Since initial Marketing Authorisation in the EU (May 2006), many procedural steps have been taken and scientific information updated after the authorisation. The refrigerated formulation is the one registered in Europe. This formulation requires higher potency VZV bulk than the frozen form and therefore more complex to produce.

The European Marketing Authorisation was initially for the frozen formulation indicated in people aged 60 and more. This has been followed by different regulatory variations. The two major ones were:

- in January 2007: manufacturing change from a frozen to a refrigerator-stable formulation (frozen no more authorised in Europe),
- in July 2007: age extension to 50 years and more.

[EMA/CHMP (2006)]

Risk management plan for ZOSTAVAX® (limited presentation):

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
9. Detection of Unanticipated Safety Signals:	1. Routine Pharmacovigilance activities 2. Three studies as part of a regulatory commitment: -Post marketing, placebo-controlled general safety study -Large-scale (20000 vaccinated participants) observational post licensure safety study -Clinical trial to assess long-term duration of protection among participants who received the vaccine during the efficacy trial, Protocol 004	--

Source: *Adapted from EMA. ZOSTAVAX®- EPAR - Product Information - Summary of Product Characteristics. 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000674/WC500053462.pdf*

[FDA 2006]:

The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine.

Discussion

Zostavax (frozen formulation) is studied in the subgroup of participants ≥60 years till 10 years post-vaccination, and in the subgroup 50 to 59 years up to 2 years post-vaccination. No new clinical studies are planned by the MAH. Long-term safety beside the above mentioned follow-up will be monitored by the obligatory updates of the registration authorities (e.g. PSUR and VAERS). Because the frozen formulation (no more authorized in Europe) has been substituted by the refrigerated formulation of Zostavax, data of both formulations should be gathered.

Zostavax is used as prevention, the intended population is large and otherwise not ill. Long-term safety is therefore extra needed.

References

1. European Medicine Agency. European Public Assessment Report (EPAR) Zostavax®. London, 19/05/2006. Scientific discussion. Available at URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000674/WC500053460.pdf
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5. Sanofi Pasteur MSD France. Marketing Authorization Holder submission file for shingles (herpes zoster) vaccine (live) Zostavax®. Submission date 12-04-2013.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

[C0005]: What are the susceptible patient groups that are more likely to be harmed?

Methods

☐ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation (REA submission file of SPMSD, SPC and EPAR's of Zostavax by CHMP/EMA) ☒
- Domain search ☒
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative

Result

[Simberkoff (2010)]

Table. Rates of Serious Adverse Events Occurring From Day 0 to 42 After Inoculation in the *Total Study Population*.

Variable	Vaccine group*		Placebo group†		Risk differences (95% CI), percentage points	P-value
Total Study	Persons With Any Serious Adverse Events, n	Persons With ≥1 Serious Adverse Events, n (%)	Persons With Any Serious Adverse Events, n	Persons With ≥1 Serious Adverse Events, n (%)		
Enrolled persons	324	255 (1.37)	320	254 (1.36)	0.01 (-0.23 to 0.25)	0.93
Age‡						
60 to 69 years	135	113 (1.12)	125	101 (1.00)	0.12 (-0.17 to 0.40)	0.41
≥70 years	189	142 (1.66)	195	153 (1.78)	-0.12 (-0.51 to 0.27)	0.55
70 to 80 years §	150	115 (1.57)	165	132 (1.80)	-0.23 (-0.65 to 0.19)	0.28
≥80 years§	39	27 (2.24)	30	21 (1.64)	0.60 (-0.49 to 1.74)	0.28

** 19 270 participants enrolled, 18 671 participants with safety follow-up.*
† 19 276 participants enrolled, 18 717 participants with safety follow-up.
‡ At time of enrollment.
§ Not a prespecified age stratum or a prespecified analysis.

Source: *Adapted from Simberkoff MS, Arbeit RD, Johnson GR, et al. Shingles Prevention Study Group. Safety of herpes zoster vaccine in the shingles prevention study:a randomized trial. Ann Intern Med 2010;152(9):545-54.*

[Simberkoff (2010)]

Table. Rates of Serious Adverse Events Occurring From Day 0 to 42 after Inoculation in the *Adverse Event Substudy*.

Type of Serious AE	Zostavax N=3345 (enrolled) N=3326 (safety follow-up)			Placebo N=3271 (enrolled) N=3249 (safety follow-up)			Risk Difference (95% CI)	P Value
	n*	n#	%	n*	n#	%		
Any SAE	83	64	1.93	55	41	1.29	0.64 (0.04; 1.28)	0.0385
Body System (COSTART)								
General body	11	10	0.30	7	7	0.22	0.08 (-0.20; 0.38)	0.50
Cardiovascular	22	20	0.61	16	12	0.37	0.24 (-0.11; 0.62)	0.161
Digestive	8	7	0.21	12	9	0.29	-0.07 (-0.37; 0.20)	0.55
Endocrine	0	0	-	0	0	-	-	-
Hemic and lymphatic	2	2	0.06	0	0	-	0.06 (-0.06; 0.24)	0.164
Metabolic/nutritional	3	3	0.09	1	1	0.03	0.06 (-0.10; 0.26)	0.33
Musculoskeletal	5	5	0.15	1	1	0.03	0.12 (-0.05; 0.35)	0.122
Nervous system	15	12	0.37	6	6	0.18	0.19 (-0.08; 0.50)	0.146
Respiratory	4	4	0.12	5	5	0.16	-0.04 (-0.28; 0.18)	0.66
Skin	6	5	0.15	4	3	0.09	0.06 (-0.15; 0.30)	0.50
Sight/sense	2	2	0.06	0	0	-	0.06 (-0.06; 0.24)	0.159
Genitourinary	5	5	0.15	2	2	0.07	0.08 (-0.12; 0.31)	0.35
Diagnostic group								
Vacular (pathology)	17	17	0.52	9	9	0.27	0.25 (-0.06; 0.61)	0.104
Vacular (functional)	10	10	0.31	9	8	0.25	0.05 (-0.23; 0.36)	0.67
Cancer	8	8	0.24	5	5	0.15	0.09 (-0.16; 0.36)	0.43
Infection	8	6	0.18	8	7	0.22	-0.04 (-0.31; 0.22)	0.71
Accident	6	6	0.18	2	2	0.06	0.11 (-0.08; 0.36)	0.183
Allergic reaction	0	0	-	1	1	0.03	-0.03 (-0.19; 0.08)	0.28
Autoimmune disorder	0	0	-	0	0	-	-	-
Other	18	17	0.51	13	9	0.30	0.21 (-0.11; 0.54)	0.178

**Number of people with any SAEs, #Number of people with at least 1 SAEs.*

Source: *Adapted from Simberkoff MS, Arbeit RD, Johnson GR, et al. Shingles Prevention Study Group. Safety of herpes zoster vaccine in the shingles prevention study:a randomized trial. Ann Intern Med 2010;152(9):545-54.*

[Fried (2010)]

Table. Subjects with ≥ 1 Serious Adverse Events (SAEs) 0 to 42 days after vaccination in the *Adverse Event Monitoring Substudy*.

Age	ZOSTAVAX vaccin n/N (%)	Placebo n/N (%)	Relative Risk (95% CI)
All	64/3,326 (1.9%)	41/3,249 (1.1%)	1.53 (1.04–2.25)
60-69 years old	22/1,726 (1.3%)	18/1,709 (1.1%)	1.21 (0.66–2.23)
70-79 years old	31/1383 (2.2%)	19/1367 (1.4%)	1.61 (0.92, 2.82)
≥80 years old	11/217 (5.1%)	4/173 (2.3%)	2.19 (0.75, 6.45)

P<0.001 for comparison of proportion of vaccine recipients with SAEs aged ≥ 80 with those aged 60–69 (Fisher exact test).
P=0.02 for comparison of proportion of vaccine recipients with SAEs aged ≥ 80 with those aged 70–79 (Fisher exact test).

Source: *Adapted from Fried R. Zoster vaccine in older adults. J Am Geriatr Soc 2010;58(9):1799-800.*

[Schmader/Levin (2012). ZEST: Efficacy and Safety Trial; n=22396; participants 50-59 years; mean follow-up: 1.3 years.

- AEs were reported by 72.8% of participants in the ZV group and 41.5% in the placebo group, with the difference primarily due to higher rates of injection-site AEs and headache.
- The proportion of participants reporting SAEs occurring within 42 days postvaccination (ZV: 0.6%; placebo: 0.5%) (relative risk 1.13; 95% CI: 0.81–1.60) and 182 days postvaccination (ZV: 2.1%; placebo: 1.9%) (relative risk: 1.11; 95% CI: 0.92–1.33) was similar between groups.
- A vaccine-related serious adverse experience was reported in 1 subject vaccinated with ZOSTAVAX (anaphylactic reaction).

[EMA/CHMP SPC (2006)]:

Several conditions are contraindicated:

- History of hypersensitivity to the active substance, to any of the excipients or trace residuals (e.g., neomycin).
- 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.
- Active untreated tuberculosis.
- Pregnancy. Furthermore, pregnancy should be avoided for 1 month following vaccination.

[EMA SPC Zostavax 2006]

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX was administered to 206 participants 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.

[Baxter 2012]
An observational post-licencure (phase IV) study was conducted at Kaiser Permanente Northern California (KPNC), A cohort of approximately 29,000 people ≥60 years of age were vaccinated with zoster vaccine from July 2006 to November 2007. Of the 386 comparisons performed for the main analysis, 4 had an increased relative risk with a

nominal p-value ≤ 0.05. After medical records review, the timing of these conditions and procedures was found to be often prior to vaccination, and no clear increase in health events was observed in the risk period following vaccination compared to later. Persons receiving zoster vaccine appeared to be in their optimal health at the time of vaccination, which led to an apparent protective effect of the vaccine for some health outcomes, due to the study design.

[SPMSD submission file (2013)]:

Table. Reports and Events in Patients 65 to 74 Years, 75 to 84 Years, and >85 Years of Age Identified 02-May-2012 to 01-Nov-2012.

Age group [years]	Reports in total	Reports on serious AE		Events in total	Serious events	
	N	n	%	N	n	%
65-74	306	23	8	761	56	7
75-85	181	12	7	403	34	8
Older than 85	31	5	16	59	14	24

Source: *Adapted from Sanofi Pasteur MSD France. Marketing Authorization Holder submission file for shingles (herpes zoster) vaccine (live) Zostavax®. Submission date 12-04-2013.*

Discussion

In the total study of SPS, no significant difference can be shown that a specific group of patient is more harmed. However, there is a trend that the oldest age group of ≥80 years has more SAEs. In contrast to the total study population, serious adverse events in the Substudy were statistically more frequent in vaccine recipients than in placebo recipients (1.93 % versus 1.29%; risk difference 0.64; 95% CI: 0.04-1.28; P = 0.038). The authors of this article [Simberkoff 2010] conclude that the observed difference in rates of serious adverse events in the vaccine recipients and placebo recipients in the substudy, although statistically significant, represents a chance occurrence in a selected subgroup and does not reflect vaccine-related events. This statement is however not supported by evidence. In the study of [Murray 2011], the relative risk for SAE for participants ≥ 80 years old is comparable between the ZV group and placebo group.

In persons aged 50-59, the proportion of participants reporting SAEs occurring within 42 days postvaccination (ZV: 0.6%; placebo: 0.5%) and 182 days postvaccination (ZV: 2.1%; placebo: 1.9%) was similar between groups.

Further analysis in a subset of the SPS participants (AE Substudy) showed a greater risk of SAEs with older age. There were 53% more SAEs overall (P=0.04) with vaccine than with placebo, but only 21% more in persons aged 60 to 69 (P=0.53), 61% more in persons aged 70 to 79 (P=0.12), and 219% more in persons aged 80 and older (P=0.19). When the two older groups were combined, there were 75% more SAEs in participants aged 70 and older with vaccine (P=0.03).

Furthermore, the authors of the SPS study did not analyze the trend toward more SAEs in older vaccinees. An analysis of SAEs according to body system did not reveal a significant difference between vaccine and placebo recipients (table 4 Simberkoff 2010), although the numbers of events was small when SAEs were broken into such fine categories, leading to a lack of statistical power. Intriguingly, 37 of the 3,326 vaccinated persons in the subgroup monitored closely for SAEs had SAEs involving the cardiovascular and nervous systems, compared with 22 of 3,249 placebo recipients (P=0.06), a difference that might have reached statistical significance after excluding the youngest age group, in whom SAEs occurred at the lowest rate [Fried 2010].

In addition, persons with a contraindication such as a compromised immune status are more likely to be harmed.

Conclusion: Individuals aged over 80 years and people with a contraindication are more susceptible to a serious adverse event after zoster vaccination. However, the oldest age group was not a prespecified subgroup within the clinical studies, further investigations are needed to elucidate the safety issue in this vulnerable group .

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9. Simberkoff MS, Arbeit RD, Johnson GR, et al. Shingles Prevention Study Group. Safety of herpes zoster vaccine in the shingles prevention study: a randomized trial. Ann Intern Med. 2010 May 4;152(9):545-54.

Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒ (subgroup analyse, age stratum not prespecified)
Not ☐

[C0007]: What are the known interactions of Zostavax use?

Methods

☐ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation (REA submission file of SPMSD, SPC and EPAR's of Zostavax by CHMP/EMA) ☒
- Domain search ☐
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative.

Result

[EMA/CHMP SPC (2006)]:

Zostavax and 23-valent pneumococcal polysaccharide vaccine should not be given together because concomitant use in a clinical trial resulted in reduced immunogenicity of Zostavax.

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

Discussion

Zostavax can be administered concomitantly with inactivated influenza vaccine as separate injections and at different body sites. This is relevant because influenza vaccine is often given to elderly people (mostly 60-65 years old) as an annual vaccination.

23-valent pneumococcal polysaccharide vaccine should not be given together with Zostavax because concomitant use will reduce immunogenicity of Zostavax.

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

References

1. European Medicine Agency. European Public Assessment Report (EPAR) Zostavax®. London, 19/05/2006. Scientific discussion. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000674/WC500053460.pdf
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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☐
Optional ☒ (depending on the setting of the vaccination for elderly in a country)

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

[C0040]: What kind of harms are there for public and environment?

Methods

☐ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation (REA submission file of SPMSD, SPC and EPAR's of Zostavax by CHMP/EMA) ☒
- Domain search ☒

- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review referred above.

Method of synthesis: Narrative

Result

[EMA/CHMP 2006]
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.

[Oxman 2005 (SPS)]
Varicella-like rashes at the injection site occurred more frequently among those in the vaccine group than among those in the placebo group, but varicella-like rashes at other sites occurred at similar rates in the two groups (table 4). There were 7 confirmed cases of herpes zoster in the vaccine group and 24 in the placebo group during the first 42 days after vaccination.

[Schmader 2012 (ZEST)]
Within the same 42-day post vaccination reporting period in the ZEST, varicella-like rashes were reported by 124 participants (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 participants who received ZOSTAVAX; however, the virus strain (wild type or Oka/Merck strain) could not be determined.

Discussion

Transmission has not been observed in the clinical trial. 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. Because of the low incidence it may be not detected yet. This is a point of attention in the future.

References

1. European Medicine Agency. European Public Assessment Report (EPAR) Zostavax®. London, 19/05/2006. Scientific discussion. Available at URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000674/WC500053460.pdf
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5. Schmader KE, Levin MJ, Gnann JW Jr 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.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

CLINICAL EFFECTIVENESS

[D0001]: What is the expected beneficial effect of vaccination with Zostavax on overall mortality?

[D0002A]: What is the expected beneficial effect on the disease-specific mortality (due to HZ/PHN)?

[D0002B1]: Who suffer the most (mortality risk)?

Methods

X See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation (REA submission file, SPC and EPAR's of Zostavax by CHMP/EMA) ☒
- Domain search ☒
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review as referred above.

Method of synthesis: narrative.

Results

[Oxman (2005)] (SPS; Shingles Prevention Study; participants ≥60 years):

Over the entire study period (median of 3.12 years of surveillance for herpes zoster), the numbers and percentages of deaths were similar in both study group.

Table. Adverse Events among All Subjects and among Those in the *Adverse-Events Substudy.**

	Vaccine group (zoster vaccine)	Placebo group	Difference in Risk (95% CI)
DEATHS			
No. of subjects	19,270	19,276	
Day of vaccination to end of study			
death	793 (4.1%)	795 (4.1%)	0.01% (-1.2 to 1.2)†
death according to age group:			
60-69 years	218 (2.1%)	246 (2.4%)	-0.80% (-2.0 to 0.4)†
≥70 years	575 (6.5%)	549 (6.2%)	0.95% (-1.2 to 3.1)†
Day of vaccination to day 42			
death	14 (0.1)	16 (0.1)	-0.01 (-0.1 to 0.1)

** The rates of death are percentages of subjects in each treatment group. Otherwise, percentages are rates weighted in proportion to the number of subjects with safety follow-up in each age group. NC denotes not calculated. Three subjects who had withdrawn from the study because of worsening health and subsequently died were included in the safety analysis.*

† The difference in risk (vaccine group-placebo group) and the 95 percent confidence intervals for deaths are based on the rates per 1000 subject-years of follow-up to account for differential follow-up among the study participants as a result of staggered enrollment. Otherwise, the differences in risk and 95 percent confidence intervals are based on an asymptotic method for the difference of two binomial proportions where the proportions are weighted according to the number of subjects with safety follow-up in each age group. Negative values for the difference in risk result when the rate in the placebo group is larger than that in the vaccine group.

Source: *Adapted from 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(22):2271-84.*

[Oxman (2005)]

The investigational zoster vaccine had low rates of serious adverse events, systemic adverse events, hospitalisation, and death. Results were similar in the two study groups, and local reactions at the vaccination site were generally mild.

No specific data about cause of death were mentioned.

[Simberkoff 2010 (SPS)].

In the table below cumulative mortality rate was shown for the time to death in all study participants. There was no significant treatment difference within age strata: log-rank p=0.20 for persons aged 60-69 years; log-rank p=0.37 for people 70 years or older. Log-rank p for overall treatment comparisons was 0.95. Log-rank p was below 0.001 for comparison of age strata 60-69 years versus 70 years or older.

Table. Cumulative mortality rates for the total study population.

Age group	Treatment group	Years of follow-up				
		0	1	2	3	4
60-69	Zostavax	10 281	10 331	10 239	7 223	2 034
	Placebo	10 223	10 323	10 245	7 231	2 081
70 years or more	Zostavax	8713	8815	8646	6415	1948
	Placebo	8692	8775	8621	6337	1942

Source: *Adapted from Simberkoff MS, Arbeit RD, Johnson GR, et al. Shingles Prevention Study Group. Safety of herpes zoster vaccine in the shingles prevention study:a randomized trial. Ann Intern Med 2010;152(9):545-54.*

Over the course of the entire study, rates of death in the total SPS population were greater in the older age stratum than in the younger age stratum. However, rates for each treatment group, both overall and by age strata, were essentially identical and did not vary appreciably over the course of the study.

[Schmader 2012 (SPS)]

There was no significant difference in deaths between placebo recipients (1.12 deaths per 100 person-years) and zoster vaccine recipients (1.03 deaths per 100 person-years) (stratified log-rank P = 0.173).

[Schmader (2012) (participants 50-59 years)]

Table. Clinical Adverse Experience Summary (day 1–42 post vaccination).

	Zoster Vaccine	Placebo	Difference (95% CI)
Subjects vaccinated and safety follow-up	11,094	11,116	
Subjects who died	1 (0%)	3 (0%)	0.0% (0,0)

Source: *Adapted from Simberkoff MS, Arbeit RD, Johnson GR, et al. Shingles Prevention Study Group. Safety of herpes zoster vaccine in the shingles prevention study:a randomized trial. Ann Intern Med 2010;152(9):545-54.*

[EMA/CHMP 2006. Scientific discussion (EPAR) of Zostavax]

Deaths

No deaths occurred in Protocols 001, 002, 003, 005, 007, and 009. In Protocol 004 (SPS), the overall mortality rate in the zoster vaccine group was similar to that in the placebo group.

[FDA 2006]

Deaths

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

Discussion

At the end of the follow-up period of the Shingles Prevention Study (median: 3.12 years), 4.1% of all participants (age 60 years and older) were deceased [Oxman 2005]. Subgroup analysis showed a more detailed picture: the total mortality in participants aged 70 years and older is significantly higher than those aged 60-69 years. 575/19270 participants (6.5%) in the Zostavax group and 549/10276 participants (6.2%) in the placebo group aged 70 years and older died. In the age group of 60-69 years old the mortality rate is lower, namely 218/19270 (2.1%) and 246/19276 (2.4%) respectively. A significant difference in the cumulative mortality rates between the age strata 60-69 years versus ≥70 years has been shown (log-rank $P < 0.001$) [Simberkoff 2010]. No specific data were available for participants of 80 years old and older. In the youngest age group of the studied population (50-59 years; [Schmader 2012]), the mortality rate in the vaccine group is even lower (1/11094; 0%).

There is no significant difference in the overall mortality between the group vaccinated with zoster vaccine (1.03 deaths per 100 person-years) and the group treated with placebo (1.12 deaths per 100 person-years) (stratified log-rank P = 0.173; all ages) [Schmader 2012, Simberkoff 2010]. Mortality due to HZ is rare, hence any effect upon mortality rate will be difficult to detect. The cumulative mortality rates between treatments within age strata are: for persons aged 60-69 years, log-rank P = 0.20; for persons 70 years or older, log-rank P = 0.37; overall treatment comparison: log-rank P = 0.95. The most common reported cause of death was cardiovascular disease. Disease-specific mortality was not reported.

In the placebo group, more cases of HZ and PHN have been observed as compared to the vaccine group (see D00011A about Incidences). Although HZ (and to a lesser extend the following PHN) are potential causes for death, the lower incidence of zoster in de vaccine group did not result in a lower number of deaths. The overall mortality rate was similar in both treatment groups.

The rates of HZ-related hospitalisation in the zoster vaccine group and the placebo group were not different. See D00011.

Conclusion:

Over the course of the entire study, rates of death in the total SPS population were higher in the older age stratum (≥70 years old: 6.5% for ZV and 6.2% for placebo) than in the younger age stratum (60-69 years old: 2.1% for ZV and 2.4% for placebo). This reflects the normal differences in mortality between the age-groups in the general population. Within each treatment, the mortality rates were similar both in the total population as in the age groups. Zostavax vaccine has not demonstrated to affect the overall mortality. Moreover, no data were available on the effect of Zostavax disease-specific mortality. This may be related to the very low number of HZ related deaths; effects of the vaccination on HZ-related mortality may be difficult to detect, especially in patients younger than 80 years. Therefore, any influence of HZ-related mortality on total mortality will be neglectable.

References

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6. Sanofi Pasteur MSD France. Marketing Authorization Holder submission file for shingles (herpes zoster) vaccine (live) Zostavax®. Submission date 12-04-2013.
7. Schmader KE, Levin MJ, Gnann JW Jr 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.
8. Schmader KE, Oxman MN, Levin MJ et al. Shingles Prevention Study Group. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. Clin Infect Dis. 2012 Nov 15;55(10):1320-8.
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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

[D0002B2]: Who suffer the most (pain)?

[D0005]: How does Zostavax affect symptoms and findings?

[D0006]: How does Zostavax affect progression of disease? (Incidence)

[D0011A]: What is the relationship between efficacy and age?

[D0011C]: What is the vaccine efficacy (VE) per age group?

Methods

☐ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation (REA submission file, SPC and EPAR's of Zostavax by CHMP/EMA) ☒
- Domain search ☒
- Other: EUnetHTA guidelines (composite endpoints) [use also Table 2 to document] ☒

Critical appraisal criteria: No qualitative tool was used for the review as referred above.

Method of synthesis: narrative and trend analysis (linear regression with constant whose, unstandardized predicted values are reported).

Result

In this results card, we combine five questions in one results card. The evidence for these related questions were partly identical. 'How does the technology affect the symptoms and findings' and 'how does it affect the progression of the disease' are covered by the handling of outcome parameters (incidence of HZ/PHN, pain scores). 'Who suffer the most (pain)' and 'the relation of the efficacy and age' referred both to age specific information. To reduce doubling of information, we choose to treat these questions as a whole.

After some explanation about methodology (how the endpoints in the clinical studies were measured), data will be shown in the following order:

- incidence of herpes zoster

- incidence of post herpetic neuralgia
- pain duration
- pain severity
- Burden of Illness (composite endpoint)

Methodology

The primary endpoint in the pivotal studies was the burden of illness (BOI) due to herpes zoster (HZ) (for SPS) and incidence of HZ (for ZEST). The secondary end point for both studies was the incidence of post herpetic neuralgia (PHN).

The **HZ BOI score** was a composite endpoint incorporating the incidence of HZ, severity and duration of the associated pain and discomfort. The diagnosis of **HZ** was confirmed by expert adjudication and viral testing by PCR. For each confirmed case of HZ, the ZBPI (Zoster Brief Pain Inventory) data were used to calculate a "HZ Severity of Illness Score", defined as the area under the ZBPI worst pain response-versus-time curve during this 182-day period (i.e., the HZ pain and discomfort severity-by-duration area-under-the-curve [AUC]). The HZ Severity of Illness Score was defined as zero for participants who did not develop a confirmed case of HZ during the study and for cases with no pain assessments.

The HZ BOI Score represented the average severity of illness among all participants in the vaccine and placebo groups; it was calculated as the sum of the HZ Severity of Illness Scores of all members of a group divided by the total number of participants (N) in that group.

PHN was defined by the presence of a typical rash and HZ-associated pain or discomfort, rated as 3 or greater (on a scale ranging from 0 to 10) and persisting or appearing more than 90 days after rash onset.

Vaccine efficacy with respect to the burden of illness due to herpes zoster (**VE BOI**) was defined as the relative reduction in the burden-of-illness score in the vaccine group as compared with that in the placebo group, and calculated as 1 minus the relative risk (i.e., 1 minus the herpes zoster burden-of-illness score in the vaccine group divided by the herpes-zoster burden-of-illness score in the placebo group).

According to the EUnetHTA guidelines, the presentation of the composite endpoints as such is not sufficient; the individual components within the composite endpoint should be reported, too. This means that BOI, incidence, severity of the pain and duration of the pain should be discussed separately.

Statistical analysis

Efficacy analyses in the clinical trials were performed with the use of a follow-up period that excluded the first 30 days after vaccination and excluded participants who withdrew and those in whom a confirmed case of herpes zoster developed within the first 30 days after vaccination. The results were essentially unchanged when participants in whom herpes zoster developed during the first 30 days were included.
Efficacy analyses in the clinical trials were therefore performed using the modified intention-to-treat (M-ITT) population, as planned in the protocol.

In this assessment we follow the study protocol and present figures of the modified ITT population. When appropriate, we'll also show ITT data if available.

Incidence of Herpes Zoster

[Oxman 2005]

In the table below effect of zoster vaccine on the BOI is presented. Analyses were performed with the use of a follow-up interval that excludes the first 30 days after vaccination and in modified ITT population (mITT). This excludes people who withdrew from the study or in whom a confirmed case of herpes zoster developed within the first 30 days after vaccination. Of three participants in whom more than one case of herpes zoster developed, only the first case was included.

Table. Effect of zoster vaccine on the burden of illness in Herpes Zoster in the modified Intention-to-Treat population.

Age group	Zostavax				Placebo				VE_{BOI} (95% CI) [%]
	N	No. of confirmed cases	BOI Score*	Incidence per 1000 Person-Year^	N	No. of confirmed cases	BOI Score*	Incidence per 1000 Person-Year^	
All	19 254	315	2.21	5.42	19 247	642	5.68	11,12	61.1 (51.1; 69.1)
60-69	10 370	122	1.50	3.90	10 356	334	4.33	10.79	65.5 (51.5; 75.5)
70 or older	8884	193	3.47	7.18	8891	308	7.78	11.50	55.4 (39.9; 66.9)

Abbreviations: ***VE_{BOI}: vaccine efficacy for the burden of illness due to herpes zoster (BOI)***

*BOI score in each treatment group was the weighted average of the observed BOI stratified according to age, with weights proportional to the total number of subjects within each age group; subjects in whom herpes zoster did not develop were assigned a score of 0 for severity of illness due to herpes zoster on the basis of the Zoster Brief Inventory, a questionnaire developed for Shingles Prevention Study.

^The incidence of herpes zoster in treatment groups was the weighted average of the observed incidence of herpes zoster stratified according to age group, with weights proportional to the total number of person-years of follow-up in each age group.

Source: *Adapted from 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(22):2271-84.*

[Oxman 2005]

The overall incidence of herpes zoster per 1000 person-years was significantly reduced by the zoster vaccine, from 11.12 per 1000 person-years in the placebo group to 5.42 per 1000 person-years in the vaccine group (P<0.001). [Difference in incidence per 1000 person-years is 5.70 (11.12 minus 5.42); not shown in this paper.] The VE HZ was **51.3%** (95% CI: 44.2-57.6).

In a time-to-event analysis, the cumulative incidence of herpes zoster was significantly lower in the vaccine group than in the placebo group (P<0.001)...

The VE HZ was **37.6%** among participants 70 years of age or older (7.18 versus 11.50) and **63.9%** among younger participants of 60-69 years old (3.90 versus 10.79; P<0.001).

[Schmader/Levin (2012)]

Table. Incidence of Confirmed Herpes Zoster Cases (in persons age 50-59 years).

Analysis	Zostavax				Placebo				VE_{BOI} (95% CI) [%]
	N	HZ cases	Total follow-up [person-years]	Estimated incidence per 1000 person-years	N	HZ cases	Total follow-up [person-years]	Estimated incidence per 1000 person-years	
ITT (entire study duration)	11211	30	15042.85	1.99	11228	99	15009.62	6.60	69,8 (54.1; 80.6)
ITT 0.0-0.5 years	11186	9	5536.77	1.62	11210	39	5541.08	7.04	76.9 (51.5; 90.2)
ITT>0.5-1.0 years	10954	13	5420.64	2.40	10953	36	5407.72	6.66	64.0 (30.4; 82.5)
ITT>1.0-1.5 years	10747	7	3513.60	2.00	10712	20	3496.06	5.72	65.2 (14.3; 87.6)
ITT>1.5 years	3743	1	571.84	1.75	3728	4	564.76	7.08	75.3 (-149.5; 99.5)
MITT	11165	26	14124.16	1.84	11189	94	14091.27	6.67	72.4 (57.0; 82.9)

Source: *Adapted from Schmader KE, Levin MJ, Gnann JW Jr, et al. Efficacy, Safety, and Tolerability of Herpes Zoster Vaccine in Persons Aged 50-59 Years. Clin Infect Dis 2012;54(7):922-8.*

[FDA (2006)], [Schmader/Levin (2012), ZEST] and [Oxman (2005) SPS]

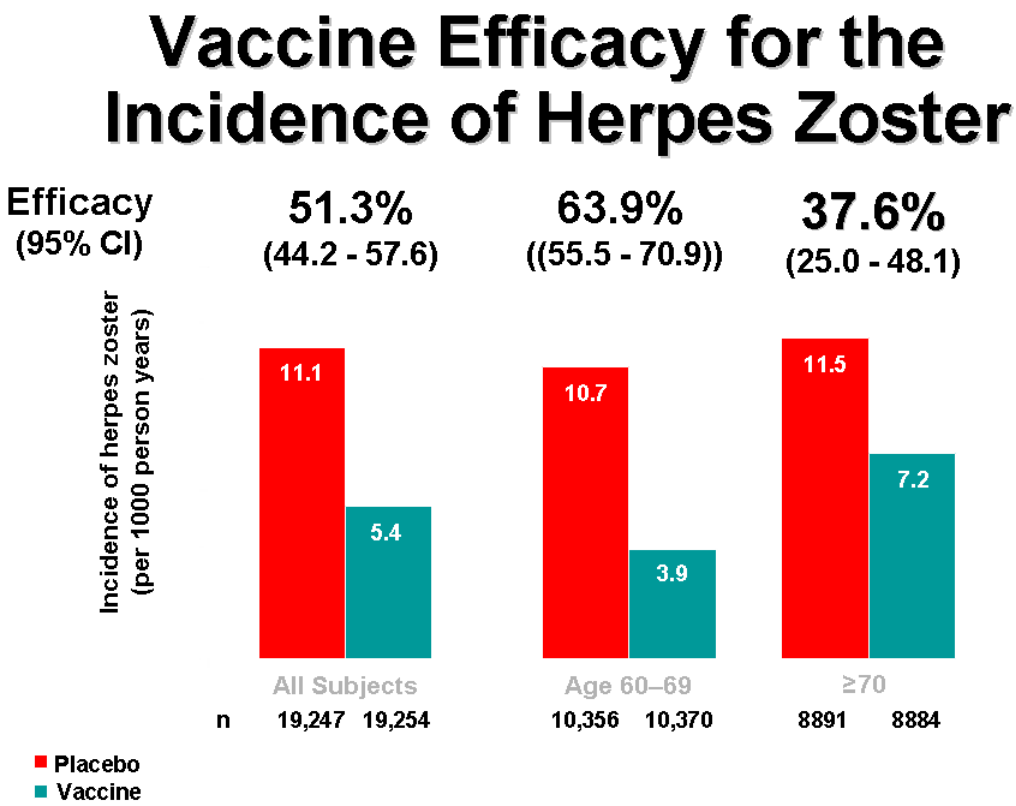
Table. Efficacy of ZOSTAVAX on HZ Incidence Compared with Placebo in the Shingles Prevention Study (≥ 60 years old) and the Efficacy and Safety Trial (50-59 years).

Age group (years)	Zostavax			Placebo			Vaccine efficacy (95% CI)
	#subjects	#HZ cases	Incidence rate of HZ per 1000 person-years	#subjects	#HZ cases	Incidence rate of HZ per 1000 person-years	
SPS study							
Overall*	19254	315	5.4	19247	642	11.1	51% (44%, 58%)
60-69*	10370	122	3.9	10356	334	10.8	64% (56%, 71%)
≥70&	8884	193	7.18	8891	308	11.50	**37.6%**
70-79*	7621	156	6.7	7559	261	11.4	41% (28%, 52%)
≥80 *	**1263**	**37**	**9.9**	**1332**	**47**	**12.2**	**18% (-29%, 48%)**
ZEST study							
50-59 $ † (ITT)	11211	30	1.994	11228	99	6.596	69.8% (54.1%, 80.6%)
50-59 $	11165	26	1.84	11189	94	6.67	72.4% (57.0–82.9)

The analysis was performed on the Modified Intent-To-Treat (MITT) population that included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of HZ within the first 30 days postvaccination.
† intent-to-treat (ITT) population, that included all subjects randomized in the ZEST.
** data FDA*
& data Oxman
$ data Schmader
*** Age strata at randomization were 60-69 and ≥70 years of age.*
Source: *Adapted from*

- *Schmader KE, Levin MJ, Gnann JW Jr, et al. Efficacy, Safety, and Tolerability of Herpes Zoster Vaccine in Persons Aged 50-59 Years. Clin Infect Dis 2012;54(7):922-8.*
- *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(22):2271-84.*
- *And FDA. ZOSTAVAX® Package insert. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM132831.pdf*

[Oxman/Levin (2008)]



Oxman MN et al. *N Engl J Med.* 2005;352:2271-2284

Figure. *Herpes zoster (HZ) vaccine efficacy for the incidence of HZ. HZ vaccine significantly reduced the overall incidence of HZ, by 51.3%, although vaccine efficacy for the incidence of HZ was reduced substantially in subjects ≥70 years of age.*
Source: *Reprinted from Journal of Infectious Diseases, Vol 197, Suppl.2, Michael N. Oxman, Myron J. Levin, Shingles Prevention Study Group "Vaccination against Herpes Zoster and Postherpetic Neuralgia" with correction for the numbers of participants (with acknowledgements to dr Oxman).* Copyright© with permission from Oxford University Press.

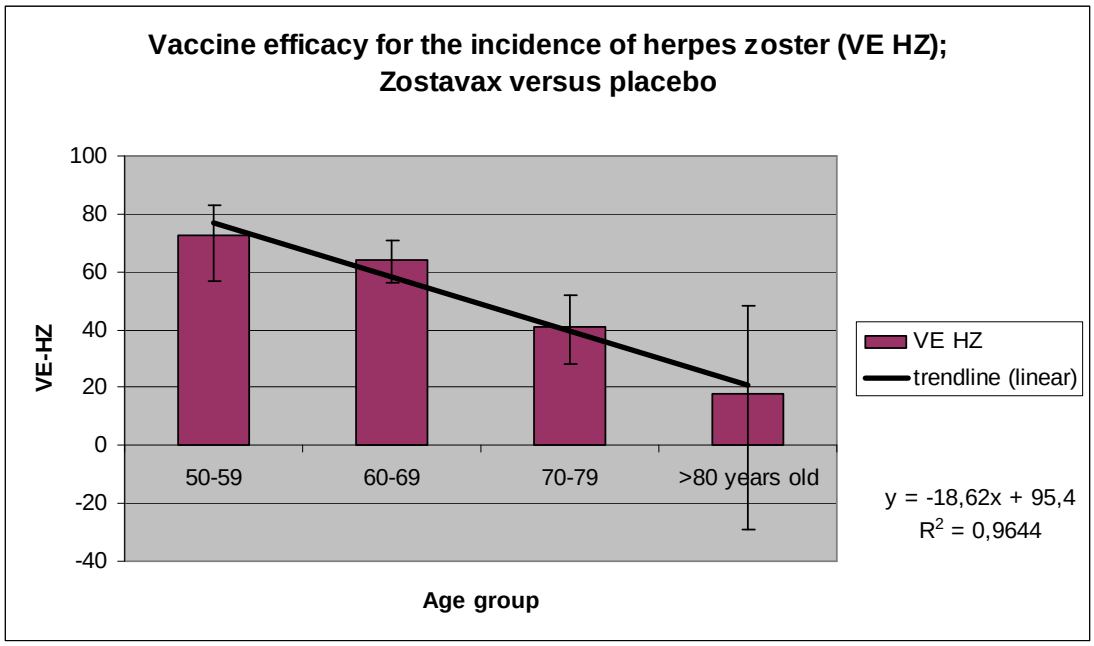
[Gagliardi (2012) Cochrane review]

Main results

The authors of this Cochrane review identified eight RCTs with a total of 52,269 participants. Three studies were classified at low risk of bias. The main outcomes on effectiveness and safety were extracted from one clinical trial with a low risk of bias. Four studies compared zoster vaccine versus placebo; one study compared high-potency zoster vaccine versus low-potency zoster vaccine; one study compared refrigerated zoster vaccine versus frozen zoster vaccine; one study compared live zoster vaccine versus inactivated zoster vaccine and one study compared zoster vaccine versus pneumococcal polysaccharide vaccine (pneumo 23).

Confirmed cases of herpes zoster were less frequent in patients who received the vaccine than in those who received a placebo: risk ratio (RR) 0.49 (95% confidence interval (CI) 0.43 to 0.56), with a risk difference (RD) of 2%, and number needed to treat to benefit (NNTB) of 50. Analyses according to age groups indicated a greater benefit in participants aged **60 to 69 years**, RR 0.36 (95% CI 0.30 to 0.45) and in participants aged 70 years and over, RR 0.63 (95% CI 0.53 to 0.75).

Trend analysis: Age dependency of the outcome VE HZ.



Data from Schmader (age group 50-59 years old) and FDA (other age groups). A good relation between age and reduced incidence of herpes zoster can be seen (R^2 =0.9644; R^2 -adj: 0.947). Vaccine efficacy for the prevention of herpes zoster decreases with age. Both regression coefficients (constant and age coefficient) are statistically significant.

Incidence of Post Herpetic Neuralgia

[Oxman (2005)]

Vaccine efficacy with respect to the incidence of postherpetic neuralgia (VE PHN) was defined as the relative reduction in the incidence of postherpetic neuralgia in the vaccine group as compared with that in the placebo group.

Table. Effect of zoster vaccine on the incidence of postherpetic neuralgia in the modified intention-to-treat population.*

	Vaccine group (zoster vaccine)		Placebo group			
	No. of Confirmed Cases of HZ with PHN/No. of Subjects	**Incidence per 1000 Person-Year†**	**No. of Confirmed Cases of HZ with PHN/No. of Subjects**	**Incidence per 1000 Person-Year†**	**Difference in incidence per 1000 Person-Year**	**VE PHN (95% CI)**
All subjects	27/19,254	0.46	80/19,247	1.38	0.92	66.5% (47.5-79.2)‡
60-69 years	8/10,370	0.26	23/10,356	0.74	0.48	65.7% (20,4-86.7)
≥70 years	19/8,884	0.71	57/8,891	2.13	1.42	66.8% (43.3-81.3)

** For the secondary end point, postherpetic neuralgia (PHN) was defined as the pain and discomfort associated with herpes zoster rated as 3 or more, on a scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine), persisting or appearing more than 90 days after the onset of herpes zoster rash. Efficacy analyses were performed with the use of a follow- up interval that excluded the first 30 days after vaccination and the modified intention-to-treat population, which excluded subjects who withdrew or in whom a confirmed case of herpes zoster developed within the first 30 days after vaccination. Of three subjects in whom more than one confirmed case of herpes zoster developed, only the first case was included. VE PHN denotes vaccine efficacy for the incidence of PHN, and CI confidence interval.*
† For the total population and the subgroups stratified according to sex, the incidence of PHN in each treatment group (vaccine or placebo) was the weighted average of the observed incidence of PHN stratified according to age group, with weights proportional to the total number of person-years of follow-up in each age group.
‡VE PHN for all subjects was the protocol-specified secondary end point.

Source: *Adapted from* 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(22):2271-84.

[Oxman (2005)]

There were 107 cases of post herpetic neuralgia, 27 in the vaccine group and 80 in the placebo group (0.46 case versus 1.38 cases per 1000 person-years, respectively; P<0.001). Overall, the VE PHN was 66.5% (95% CI: 47.5 to 79.2).

No significant differences in the VE PHN can be observed when the results were stratified according to age (VE 65.7% for 60-69 years and 66.8 % for ≥ 70 years). However, the absolute difference in incidence per 1000 person-years between both arms differed: 0.92 for the total population, 0.48 for the group 60-69 years and 1.41 for the oldest group of ≥ 70 years.

In a time-to-event analysis, the cumulative incidence of postherpetic neuralgia was significantly lower in the vaccine group than in the placebo group (P<0.001).

[Schmader (2012)]

The study only measured acute pain and provided no data on the effect of Zostavax on PHN in this age group (50-59 years old). The sample size needed to determine effect on PHN would be prohibitively large. Because of the low incidence of PHN in participants aged 50-59 years old, the effect of Zostavax on the incidence of PHN was not studied in this age group.

Oxman/Levin (2008)]

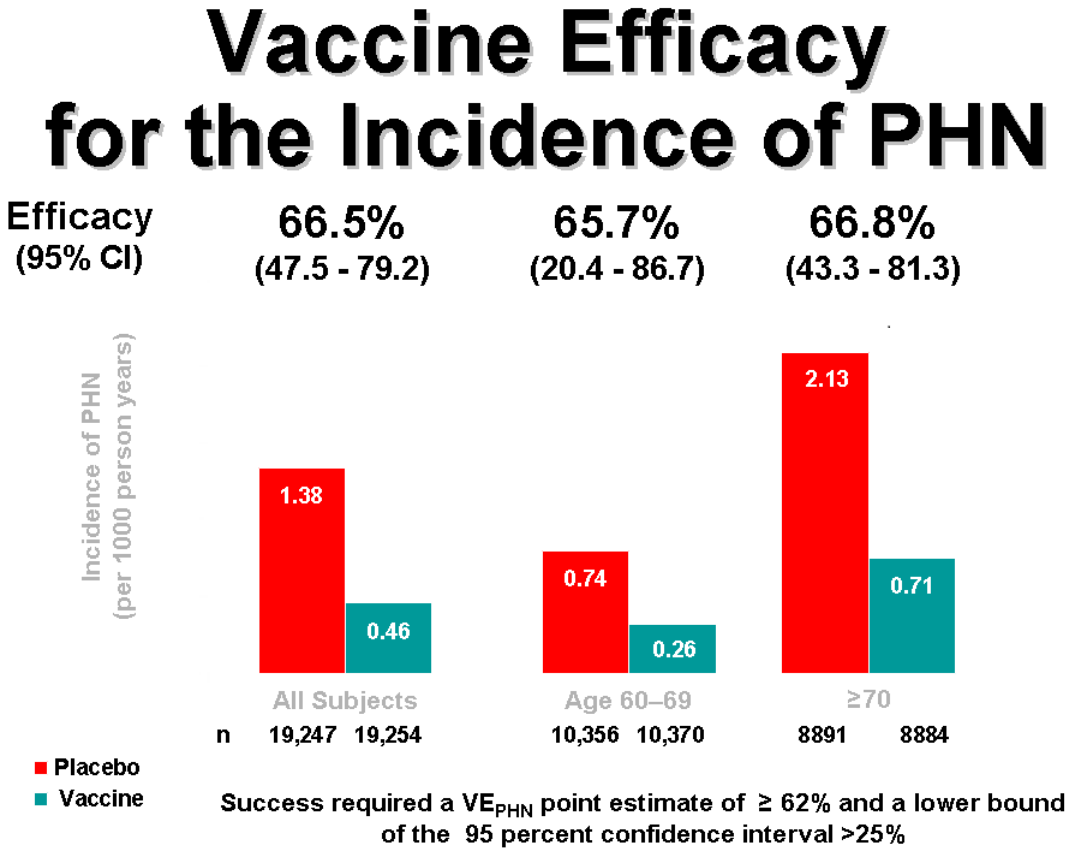


Figure. *Herpes zoster (HZ) vaccine efficacy for the incidence of post herpetic neuralgia (PHN). HZ vaccine significantly reduced the incidence of PHN, by approximately two-thirds, in all subjects and in both age strata. It is important to note that this reduction is among all subjects and not just those with HZ.*

Source: Reprinted from *Journal of Infectious Diseases, Vol 197, Suppl.2, Michael N. Oxman, Myron J. Levin, Shingles Prevention Study Group "Vaccination against Herpes Zoster and Postherpetic Neuralgia" with correction for the numbers of participants (with acknowledgements to dr Oxman).* Copyright© with permission from Oxford University Press.

[FDA (2006)]

Table. Postherpetic Neuralgia (PHN)* in the Shingles Prevention Study**

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

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

Source: *Adapted from FDA. ZOSTAVAX® Package insert. Available at:* http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM132831.pdf

[FDA 2006; Health Canada]]

Although using the same source of data (SPS), FDA used other calculations to evaluate vaccine efficacy. Efficacy against PHN is estimated **in participants who develop HZ post vaccination** and not in the total population.

According to the FDA, vaccine efficacy against PHN in participants who develop HZ post vaccination (95% CI) was: 39% (7% to 59%) for the total group; 5% (-107% to 56%) for 60-69 years old; 55% (18% to 76%) for 70-79 and 26% (-69% to, 68%) for 80 years old and older. This means that the vaccine, for the prevention of PHN in patients who already developed HZ, is most active in individuals 70-79 years (55%), somewhat active in ≥80 years old (26%), and almost not active (5%) in the age group of 60-69 years old. According to Health Canada, the vaccine efficacy against PHN in participants who developed HZ at least 30 days post-vaccination in individuals for 70 years and older was 47% (13% to 67%).

[Chen 2011 (Cochrane review)]

Main results of the review: One trial, which involved 38,546 participants and compared vaccination with placebo, met the inclusion criteria of Cochrane. This included study (SPS trial) was of high quality. However, its participants were all aged 60 years or more and most of them were white, which may mean that its findings are not applicable to all populations. The vaccine was effective in decreasing the incidence of herpes zoster, but a reduction in the incidence of postherpetic neuralgia beyond its effect on the incidence of herpes zoster was not statistically significant.

Conclusion of Chen: There is insufficient direct evidence from specialised trials to prove the efficacy of vaccine for preventing postherpetic neuralgia beyond its effect on reducing herpes zoster, although vaccination may be efficacious and safe for preventing herpes zoster and thus reduce the incidence of postherpetic neuralgia in adults aged 60 years or older.

Table. Data for the forest plot of comparison: 1 Incidence of PHN, outcome 1.1 Vaccine group versus placebo group.

	Vaccine		Placebo		Weight	Risk ratio
Study or subgroup	**Events**	**total**	**events**	**total**		**M-H, Fixed, 95% CI**
SPS 2005	17	19254	54	19247	100%	0.31 (0.18, 0,54)
Total (95% CI)		19254		19247	100%	0.31 (0.18, 0,54)
Total events	17		54			
Heterogeneity: not applicable Test for overall effect: Z=4.16 (P=0<0.0001)						

Source: *Adapted from Chen N, Li Q, Zhang Y, et al. Vaccination for preventing postherpetic neuralgia. Cochrane Database Syst Rev 2011:CD007795*.

Table. Data for the forest plot of comparison: 2 Incidence of PHN **in participants developed herpes zoster,** outcome: 2.1 Vaccine group versus placebo group.

	Vaccine		Placebo		Weight	Risk ratio
Study or subgroup	**Events**	**total**	**events**	**total**		**M-H, Fixed, 95% CI**
SPS 2005	17	315	54	642	100%	0.64 (0.38, 1.09)
Total (95% CI)		315		642	100%	0.64 (0.38, 1.09)
Total events	17		54			
Heterogeneity: not applicable Test for overall effect: Z=1.65 (P=0.10)						

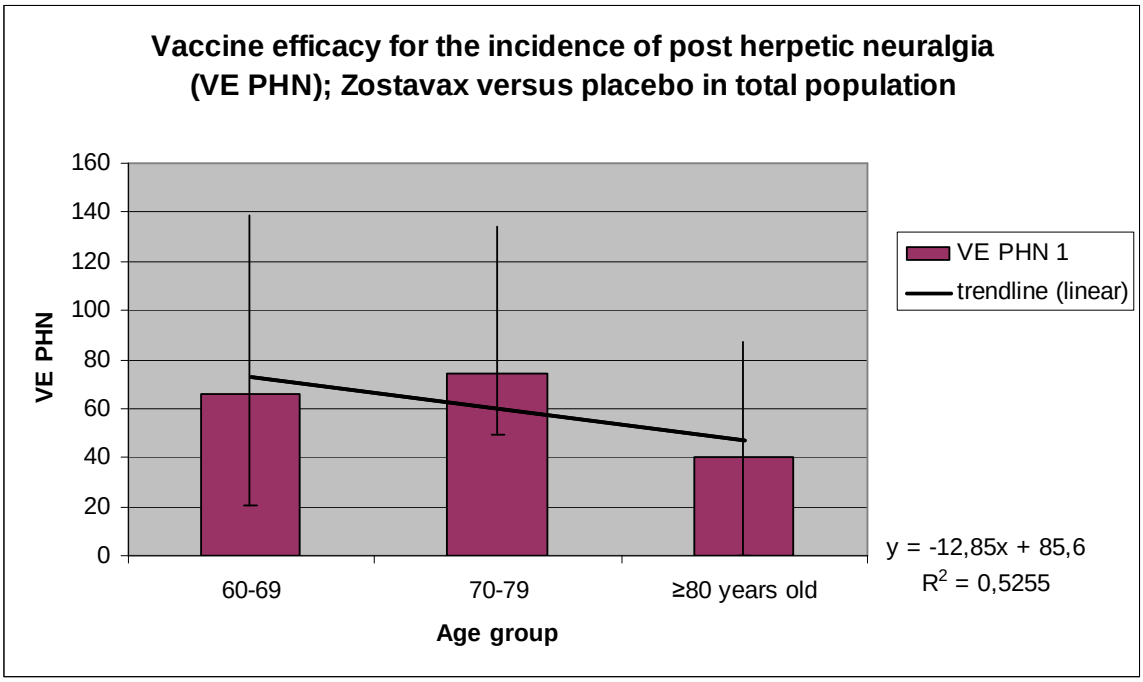
Source: *Adapted from Chen N, Li Q, Zhang Y, et al. Vaccination for preventing postherpetic neuralgia. Cochrane Database Syst Rev 2011:CD007795*.

Vaccine efficacy for Incidence of PHN (VE PHN) was defined as the relative reduction (1 minus relative risk) in the incidence of PHN in the vaccine group compared with the placebo group. In this case the VE PHN in the total study population can be calculated as 69% (100*(1-0,31)) and the VE PHN in those who develop HZ after vaccination can be calculated as 36% (100*(1-0.64)).

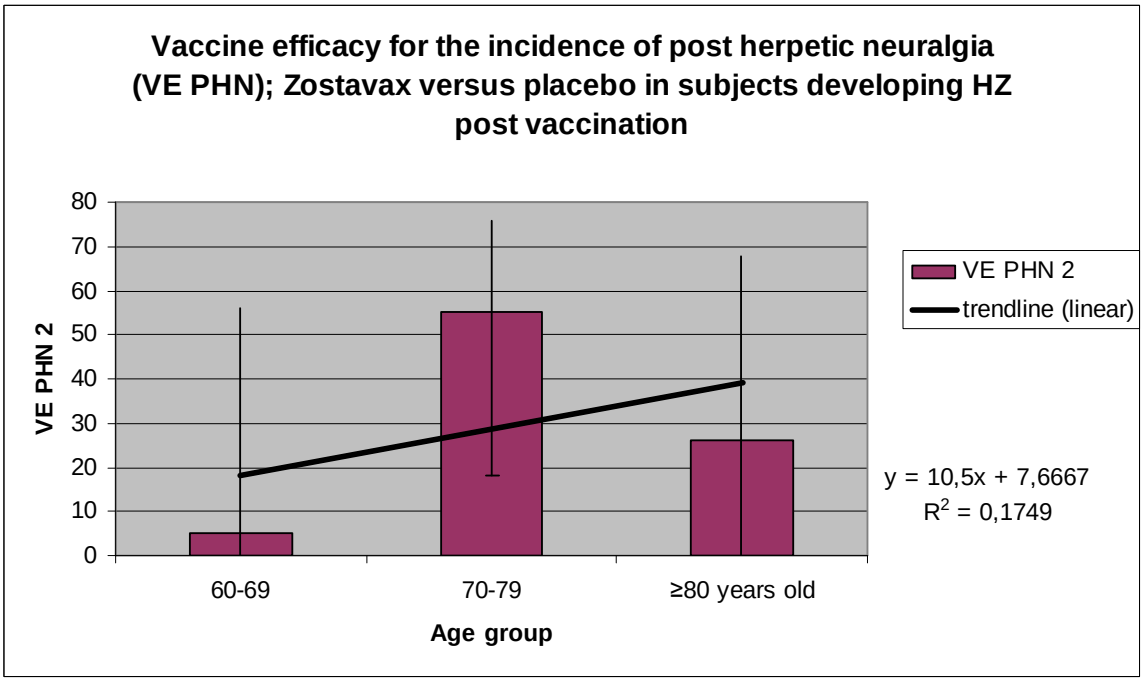
Note: The number of event (PHN cases) in the Cochrane review is lower as compared to the publication of Oxman and FDA for both study arms. Chen: n=17 (Zostavax) and n=54 (placebo). Oxman/FDA: n=27 (Zostavax) and n=80 (placebo). The most important reason is probably a more strict definition of PHN (persisting or recurring pain more than 120 days instead of 90 days). In the paper of Chen it was not motivated why a more strict definition of PHN was used compared to the definition used by [Oxman 2005]. Also, no data stratified by age has been presented.

Trend analyses: VE PHN in different age groups

1) As compared to the total population of vaccines: data from Oxman 2005 (60-69 years old) and manufactrurer (other age groups).



2) As compared to participants who developed herpes zoster after vaccination: all data from FDA.



In both cases, data of 3 age groups were available. Based on the data shown above, no correlation can be shown.

Duration of the pain

[Oxman (2005)]
The median duration of pain and discomfort among participants with confirmed cases of herpes zoster was significantly shorter in the vaccine group than in the placebo group (21 days versus 24 days, P=0.03).

[EMA/CHMP (2006)]
Following vaccination, the duration of clinically significant pain associated with HZ in both age groups was significantly reduced (20 days versus22 days, p-value < 0.001). However, less significant pain (<3) a reduction was observed only in the younger age

group (30 versus 36 days), while for the group of older participants no difference was found compared to the placebo group (<3; median duration 41 days for both groups).

[FDA 2006]

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

Severity of the pain

There is no public information specific about the severity of the pain, such as the measured pain scores, variation of the scores over the course of the study, pain in different age groups, effect of pain medication on the pain scores etcetera. Because PHN is based on the existence of long-lasting pain and discomfort, the persistence of PHN reflect to the experienced pain. In the absence of specific data about severity of the pain, data about the persistence of PHN is shown here.

[Oxman (2005)]

Vaccine efficacy for Incidence of PHN (VE PHN) was defined as the relative reduction (1 minus relative risk) in the incidence of PHN in the vaccine group compared with the placebo group.

Table. Effect of Zoster Vaccine on **Persistence** of Postherpetic Neuralgia in the Modified Intention-to-Treat Population.*

	Vaccine group (zoster vaccine)		Placebo group		Difference in incidence per 1000 Person-Year	VE PHN (95% CI)
	No. of Confirmed Cases of HZ with PHN/ No. of Subjects	Incidence per 1000 Person-Year†	No. of Confirmed Cases of HZ with PHN/ No. of Subjects	Incidence per 1000 Person-Year†		
Persistence of PHN among all subjects§						
30 days	81	1.39	196	3.39	2.00	58.9% (46.6–68.7)
60 days	45	0.77	113	1.96	1.19	60.4% (43.6–72.6)
90 days	27	0.46	80	1.38	0.92	66.5% (47.5–79.2)‡
120 days	17	0.29	54	0.93	0.64	68.7% (45.2–83.0)
182 days	9	0.16	33	0.57	0.41	72.9% (42.1–88.6)

** For the secondary end point, postherpetic neuralgia (PHN) was defined as the pain and discomfort associated with herpes zoster rated as 3 or more, on a scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine), persisting or appearing more than 90 days after the onset of herpes zoster rash. Efficacy analyses were performed with the use of a follow- up interval that excluded the first 30 days after vaccination and the modified intention-to-treat population, which excluded subjects who withdrew or in whom a confirmed case of herpes zoster developed within the first 30 days after vaccination. Of three subjects in whom more than one confirmed case of herpes zoster developed, only the first case was included. VE PHN denotes vaccine efficacy for the incidence of PHN, and CI confidence interval.*

† For the total population and the subgroups stratified according to sex, the incidence of PHN in each treatment group (vaccine or placebo) was the weighted average of the observed incidence of PHN stratified according to age group, with weights proportional to the total number of person-years of follow-up in each age group.

‡VE PHN for all subjects was the protocol-specified secondary end point.

§ PHN was defined as the pain and discomfort associated with herpes zoster that was rated as 3 or more persisting or appearing more than 30, 60, 90, 120, and 182 days after the onset of herpes zoster rash.

***Source:** 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(22):2271-84.*

[Oxman (2005)]

- The mean herpes-zoster severity-of-illness score (AUC) among participants with confirmed cases of herpes zoster was significantly lower in the vaccine group than in the placebo group (141.2 versus 180.5, P=0.008). The herpes-zoster severity-of-illness score is also a composite outcome. It is defined as the area under the curve

(AUC) of herpes-zoster pain plotted against time during the 182-day period after the onset of rash.

- Specific data about the severity of the pain are not available. Hence also no data for pain severity in relation to age.

Burden of illness

[Oxman 2005]

Table. Effect of Zoster Vaccine on the Burden of Illness in Herpes Zoster in the Modified Intention-to-Treat Population.

Age group	Zostavax				Placebo				VE_{BOI} (95% CI) [%]
	N	No. of confirmed cases	BOI Score*	Incidence per 1000 Person-Year^	N	No. of confirmed cases	BOI Score*	Incidence per 1000 Person-Year^	
All	19 254	315	2.21	5.42	19 247	642	5.68	11,12	61.1 (51.1; 69.1)
60-69	10 370	122	1.50	3.90	10 356	334	4.33	10.79	65.5 (51.5; 75.5)
70 or older	8884	193	3.47	7.18	8891	308	7.78	11.50	55.4 (39.9; 66.9)

Abbreviations: ***VE_{BOI}: vaccine efficacy for the burden of illness due to herpes zoster (BOI)***

**BOI score in each treatment group was the weigted average of the observed BOI stratified according to age, with weights proportional to the total number of subjects within each age group; subjects in whom herpes zoster did not develop were assigned a score of 0 for severity of illness due to herpes zoster on the basis of the Zoster Brief Iventory, a questionnaire developed for Shingles Prevention Study.*

^The incidence of herpes zoster in treatment groups was the weighted average of the observed incidence of herpes zoster stratified according to age agroup, with weights proportional to the total number of person-years of follow-up in each age group.

Source: *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(22):2271-84.*

The use of the zoster vaccine reduced the burden of illness due to herpes zoster in the total study population by 61.1% (95% CI: 51.5-69.1; P<0.001). Specific data for both age strata were analysed too: for 60–69 years is the burden of Illness in herpes zoster: 65.5% (95% CI: 51.5–75.5); for ≥70 years is the VE BOI 55.4% (95% CI: 39.9–66.9).

[Oxman/Levin (2008)]

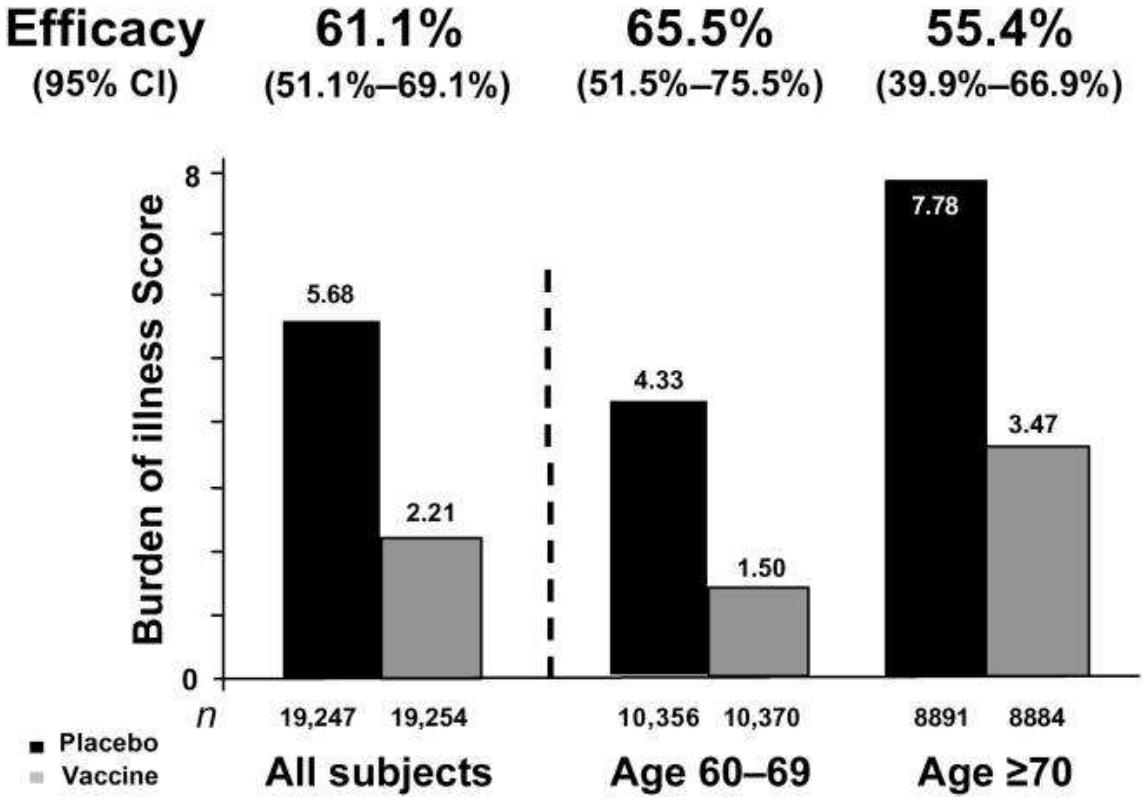


Figure. *Herpes zoster (HZ) vaccine efficacy for the HZ Burden of Illness (HZ BOI). The primary end point of the Shingles Prevention Study was the HZ BOI, a severity-by-duration measure of the total pain and discomfort associated with HZ in the population of study subjects. For each confirmed case of HZ, responses to the "worst pain in the last 24h" question in the Zoster Brief Pain Inventory were used to calculate an HZ Severity-of-Illness Score, defined as the area under the curve of HZ pain and discomfort plotted against time during the 182-day period after the onset of HZ rash. Subjects with HZ had HZ Severity-of-Illness Scores ranging from 0 to 1813. Increasing HZ Severity-of-Illness Scores are highly correlated with a decrease in the health-related quality of life and in functional status of older adults [44]. An HZ Severity-of-Illness Score of 0 was recorded for subjects in whom HZ did not develop during the study period. The HZ BOI Score represents the average HZ Severity-of-Illness Score among all subjects in the vaccine or placebo groups; it was calculated as the sum of the HZ Severity-of-Illness Scores of all members of a group divided by the total no. of subjects in the group.*
Source: Reprinted from *Journal of Infectious Diseases, Vol 197, Suppl.2, Michael N. Oxman, Myron J. Levin, Shingles Prevention Study Group "Vaccination against Herpes Zoster and Postherpetic Neuralgia"*. Copyright© with permission from Oxford University Press.

[Schmader/Levin (2012)]

To summarize HZ acute pain score over time, severity-by-duration scores were utilized. For each confirmed HZ case, the severity-by-duration score of HZ acute pain is the area under the curve (AUC) score defined by the ZBPI HZ pain response curve from HZ onset date through **day 21** after HZ onset.

The mean severity-by-duration pain score among all the participants in the ZV group was lower (0.13) than the placebo group (0.49). The estimated relative reduction in this pain score between the 2 groups was 73.0% (95% CI: 52.7%–84.6%).

[SPMSD submission file (2013)]

Table. Efficacy (% [95% CI]) of zoster vaccine per age on HZ (data from SPS and ZEST) [131; 170; 207; 219; 223]

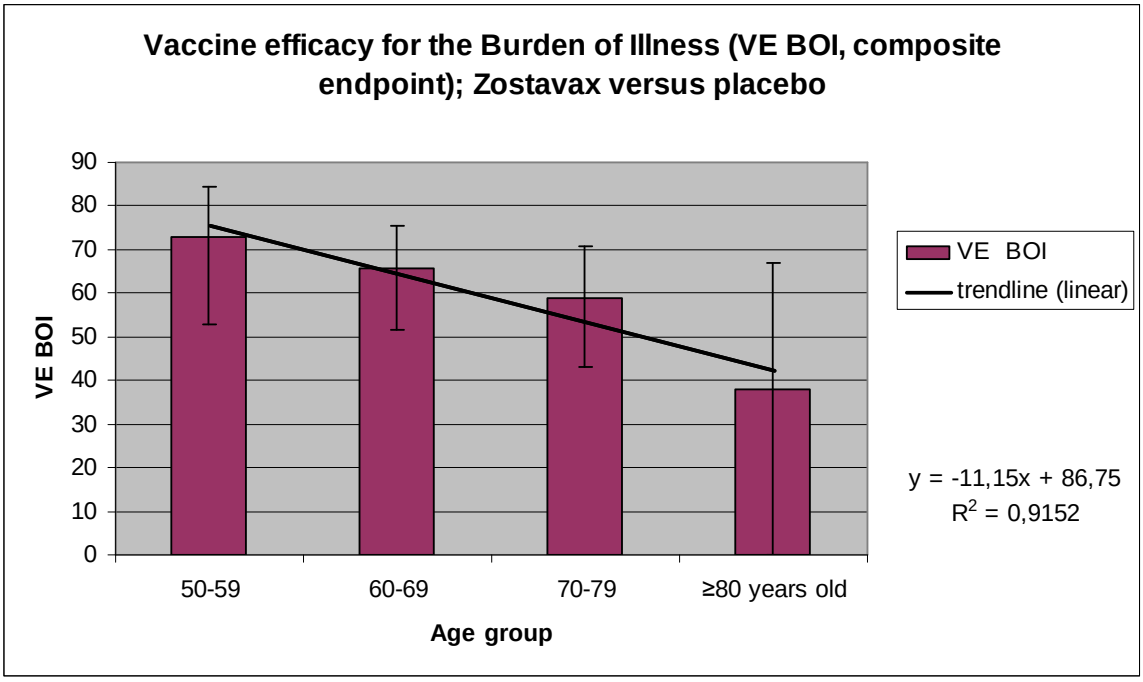
Age group (years)	50-59	≥60	60-69	≥70	70-79	≥80
Vaccinated N=	11,211	19,254	10,370	8,884	7,621	1,263
Placebo N=	11,228	19,247	10,356	8,891	7,759	1,332
VE HZ incidence	70% [54%;81%]	51% [44%;58%]	64% [56%;71%]	38% [25%;48%]	41% [28%;52%]	18% [<0%;48%]
VE PHN incidence	Not available	67% [48%;79%]	66% [20%;87%]	67% [43%;81%]	74% [49%;87%]	40% [<0%;67%]
VE PHN proportion among HZ cases	Not available	39% [7%;59%]	5% [<0%;56%]	47% [13%;67%]	55% [18%;52%]	26% [<0%;68%]
VE BOI	73%* [53%;85%]	61% [51%;69%]	66% [52%;76%]	55% [40%;67%]	59% [43%;71%]	38% [<0%;67%]

** BOI in 50-59 is calculated over a 21-day period following HZ rash onset (whereas in ≥60 years, BOI is calculated over 182 day-period) – unpublished for ≥80.*

Source: *Adapted from Sanofi Pasteur MSD France. Marketing Authorization Holder submission file for shingles (herpes zoster) vaccine (live) Zostavax®. Submission date 12-04-2013.*

According to SPMSD, there are no age specific information about the duration and severity of the pain. Also specific information about pain in participants older than 80 years is not published. Note: data of age group 50-59 in the table of SPMSD are ITT figures and not mITT (other published data).

Trend analysis: Age dependency of the compsite outcome VE BOI.



Data from Schmader (age group 50-59), Oxman 2005 (60-69 years old) and the MAH (the other 2 age groups). A good relation between age and reduction of the Burden of Illness was shown (R^2 =0,9152; R^2 –adj: 0.873). Both regression coefficients are statistically significant. Vaccine efficacy for the Burden of Illness decreases with age.

In summary

The efficacy of ZOSTAVAX as compared to placebo on HZ Incidence and on PHN incidence can be summarized as followed:

Age group (years)	Vaccine efficacy for incidence of HZ (95% CI)	Vaccine efficacy for incidence of PHN in total study population (95% CI)	Vaccine efficacy for incidence of PHN in those who develop HZ after vaccination (95% CI)	Vaccine efficacy for Burden of Illness (95% CI)
50-59	72.4% (57.0;82.9)	No data	No data	73.0% (52.7;84.6)*
60-69	64% (56;71)	65.7% (20.4;86.7)	5% (-107;56)	65.5% (51.5;75.5)
70-79	41% (28;52)	74% (49;87)*$*	55% (18;76)	59% (43;71) $
Overall (≥60)	51% (44;58)	66.5% (47.5;79.2) 69% (46;82)#	39% (7;59) 36% (-9;62)#	61.6% (51.1;69.1)
≥70	37.6% (25.0;48.1)	66.8% (43.3;81.3)	47% (13;67) $	55.4 % (39.9;66.9)
≥80	18% (-29;48)	40% (<0;67)$	26% (-69;68)	38% (<0;67)$

** BOI in 50-59 is calculated over a 21-day period following HZ rash onset (whereas in ≥60 years, BOI is calculated over 182 day-period.*
$ unpublished data from SPMSD
Results are based on the more strict selection of PNH cases (persisting or recurring pain more than 120 days instead of 90 days) in the Cochrane Study of Chen et al. Vaccine efficacy (%) was calculated as 100*(1-Risk Ratio)

Discussion

The vaccine efficacy of Zostavax in reducing the risk of developing zoster has been studied in two pivotal clinical trials: SPS for participants of 60 years and older, and ZEST for participants of 50-59 years old (incidence PHN was not assessed in this age group). In a time-to-event analysis, the cumulative incidences of herpes zoster and of postherpetic neuralgia were both significantly lower in the vaccine group than in the placebo group (P<0.001).

Incidence HZ:

The incidence of HZ (incidence per 1000 persons-years) increased with age both in the vaccine group (1,84 for 50-59 years old; 3.9 for 60-69 years old; 6.7 for 70-79 years old; and 9.9 for ≥80 years old) as well as the placebo group (6.67 for 50-59 years old; 10.8 for 60-69 years old; 11.4 for 70-79 years old; and 12.2 for ≥80 years old). Although the incidence in the intervention group is lower.

In the modified intention-to-treate population, Zostavax significantly reduced the risk of developing zoster when compared with placebo. The vaccine efficacy for the prevention of HZ was the highest for those participants 50-59 years of age and declined with increasing age.

The vaccine efficacy for HZ reduction are: 72% (50-59 years old), 64% (60-69 years old), 41% (70-79 years old) and 18% (≥80 years old). This age dependency of this HZ lowering effect was confirmed by a trend analysis. A good relation between age and reduced incidence of herpes zoster can be seen (R^2 =0,9644; R^2-adj: 0.947).

According to the Cochrane review (Gagliardi 2012), the number needed to treat to benefit (NNTB) is 50. However, this is an estimation of the overall group. Information about age specificity is not available.

Incidence PHN:

The incidence of PHN increased with age both in the vaccine group as well as the placebo group. In the vaccine group is that 0.26 per 1000-persons-years for 60-69 years old and 0.71 per 1000-persons-years for ≥70 years. In the placebo group is the incidence per 1000-persons-years respectively 0.74 and 2.13.

The vaccine efficacy of Zostavax in reducing the risk of post herpetic neuralgia can be expressed in different ways, either towards the total study population (Oxman 2005) or towards participants who develop HZ after vaccination (FDA and Chen).

In the SPS study, there were 107 cases of post herpetic neuralgia, 27 participants in the vaccine group and 80 participants in the placebo group (0.46 case versus 1.38 cases per 1000 person-years, respectively; P<0.001). Overall, the VE PHN was 66.5% (95% CI: 47.5 to 79.2; *P*<0.001) as compare to the total population. There were no significant

differences in the VE PHN when the results were stratified according to age. Vaccine efficacy in the age group of 50-59 was not investigated.

Within the participants who develop HZ after vaccination, the vaccine efficacy is lower. The vaccine efficacy is in that case 39% (95% CI: 7 to 59%) overall; 5% (95% CI: -107 to 56%) for 60-69 years old; 55% (95% CI: 18 to 76%) for 70-79 years old and 26% (95% CI: -69 to 68%) for 80 years old and older. This means that the vaccine, for the prevention of PHN, is most active in individuals 70-79 years (55%), somewhat active in ≥80 years old (26%), and almost not active (5%) in the age group of 60-69 years old. A correlation between age and effect can not be shown.

The Cochrane review [Chen 2011] came to the conclusion that a reduction in the incidence of postherpetic neuralgia beyond its effect on the incidence of herpes zoster by Zostavax is not statistically significant. However, the number of events (PHN cases) used was lower that those in the publication of Oxman and the FDA, due to a more strict definition of PHN (persisting or recurring pain more than 120 days instead of 90 days).

Duration and severity of pain

According to the publication of Oxman (2005), zoster vaccine leads to a shortening of the pain with 3 days (21 days versus 24 days, P=0.03). However, according to the FDA and the EMA, this effect is even less (2 days, i.e. 20 days versus 22 days). Because specific data about the severity of the pain solely is not available, the clinical relevance of a reduction of 2 to 3 days is not clear.

Moreover, a reduction of less significant pain (pain score <3) was observed only in the younger age group (30 versus 36 days), while for the group of older participants no difference was found compared to the placebo group (<3; median duration 41 days for both groups).

Burden of illness

The use of the zoster vaccine reduced the burden of illness (BOI) due to herpes zoster also in an aged dependent way. The vaccine efficacy of the BOI are: 73.0% for participants 50-59 years old; 65.5% for participants 60-69 years old; 59% for participants 70-79 years old and 38% for participants ≥80 years old. A good relation between age and reduction of the BOI was shown (R^2 =0,9152; R^2-adj: 0.873). Both regression coefficients are statistically significant. Vaccine efficacy for the BOI decreases with age.

VE BOI is a composite endpoint; therefore it is unclear whether the reduction in the BOI was caused by a reduction in the incidence, duration of the pain, intensity of the pain or a combination of these parameters. The VE BOI is calculated by a complex method to summarize the effect of HZ over time. To capture degree and duration of the effect of HZ, a ''burden of interference'' score is calculated from the area under the curve created when the effect of HZ is plotted against time. In essence, time is used as a multiplier of the effect of HZ. A problem with this method is that small differences in HZ pain-related measures over a long period of time can have a large effect on this score but may not be clinically meaningful. This would lead to an overestimate of vaccine effectiveness. This problem is also addressed by Fried.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☒
Important ☐
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

[D0011B]: What is the relationship between efficacy and co medication/co vaccination?

Methods

☐ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation (REA submission file, SPC and EPAR's of Zostavax by CHMP/EMA) ☒
- Domain search ☒
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review as referred above.

Method of synthesis: narrative.

Result

[Kerzner (2007)]

Concomitant administration of Zostavax and **inactivated Influenza vaccine** (three vaccine strains; 2005–2006 influenza season) in adults ≥50 years (n=762):

VZV Ab GMTs (varicella zoster virus antibody geometric mean titers) 4 weeks post vaccination for the concomitant and sequential groups were 554 and 597 gpELISA U/mL, respectively. The estimated VZV Ab GMT ratio was 0.9 (95% confidence interval (CI): 0.8–1.0), indicating **noninferior** (P<0.001 for the null hypothesis of GMT ratio <0.67) responses. Estimated VZV Ab GMFR (geometric mean fold rise) from baseline in the concomitant group was 2.1 (95% CI=2.0–2.3), indicating acceptable fold rise. Estimated

GMT ratios (concomitant/sequential) for influenza strains A(H1N1), A(H3N2), and B were 0.9 (95% CI:0.8–1.1), 1.1 (95% CI=0.9–1.3), and 0.9 (95% CI=0.8–1.1), respectively, and SCRs (influenza Seroconversion Rates) were comparable across both groups, with more than 85% achieving titers of 1:40 or greater, meeting regulatory criteria.

CONCLUSION of Kerzner: ZOSTAVAX and influenza vaccine given concomitantly are generally well tolerated in adults aged 50 and older. Antibody responses were similar whether ZOSTAVAX and influenza vaccine were given concomitantly or sequentially.

Incidence of HZ/PHN and burden are not measured in this study.

[MacIntyre (2010)]

Concomitant administration with **pneumococcal vaccines (PP V23)** in adults ≥60 years (n=473):

Four weeks postvaccination with ZV, VZV Ab response in concomitant group was not similar to nonconcomitant group; estimated VZV GMT ratio [concomitant/ nonconcomitant] was 0.70 (95% CI, 0.61–0.80). VZV Ab response was acceptable in concomitant group; estimated geometric mean fold rise (GMFR) from baseline was 1.9 (95% CI, 1.7–2.1). Pneumococcal polysaccharides serotype-specific Ab responses were similar in both groups.

CONCLUSION of McIntyre: In summary, VZV GMT Ab response induced by zoster vaccine (ZV) administered concomitantly with pneumococcal polysaccharide vaccine was **inferior** to that induced nonconcomitantly. These results indicate that, to avoid a potential decrease in ZV immunogenicity, ZV & PP V23 should not be given concomitantly.

[EMA, SPC Zostavax (2006)]

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

In a double-blind, placebo-controlled, randomized clinical trial [Mill 2010], ZOSTAVAX was administered to 100 participants 50 years of age or older with a history of herpes zoster (HZ) prior to vaccination to assess immunogenicity of ZOSTAVAX.

ZOSTAVAX induced a significantly higher VZV-specific immune response 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 versus 393 gpELISA units/ml). VZV antibody responses were generally **similar** in participants 50 to 59 compared to participants ≥60 years of age.

[EMA, SPC Zostavax (2006)]

Based on limited data from 2 clinical trials [Macaladad 2007, Diaz 2006] that enrolled **VZV-seronegative** or low seropositive participants (27 participants 30 years of age or older received live attenuated zoster vaccine). According to the EMA, the responses (IFN-gamma ELISA and the VZV-specific ELISA) were **higher** in individuals who were seropositive at baseline as compared to seronegative individuals.

[EMA SPC Zostavax 2006]

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX was administered to 206 participants 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.

[EMA SPC Zostavax (2006)]

The efficacy of ZOSTAVAX have **not** been established in adults who are known to be **infected with HIV** with or without evidence of immunosuppression. immunosuppression due to HIV/AIDS is denominated as a contraindication. A clinical trial is ongoing (clinical trial NCT00851786).

Summary of the risk management plan (partly):

Safety issue Proposed pharmacovigilance	activities	Proposed risk minimisation activities
Lack of data in immunocompromised subjects.	The applicant will study the safety and immunogenicity in HIV-infected individuals and subjects on chronic systemic corticosteroid therapy.	Contraindications in primary and acquired immunodefiscuiency states, in case of immunosuppressive therapy or active untreated tuberculosis (see SPC section 4.3). Warnings in section 4.4 and 5.1 with regard to adults infected by HIV and subject with immunocompromised subjects.

[EMA, SPC Zostavax (2006)]

Immunogenicity in patients on **chronic/maintenance systemic corticosteroids**

In a double-blind, placebo-controlled, randomized clinical trial, ZOSTAVAX was administered to 206 participants 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 of ZOSTAVAX.

Compared with placebo, ZOSTAVAX induced a **higher** VZV-specific gpELISA antibody GMT at 6 weeks postvaccination (GMT of 531.1 versus 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.

[Langan 2013]

A cohort study of 766,330 fully eligible individuals aged ≥65 years was undertaken in a 5% random sample of Medicare who received and did not receive zoster vaccination between 1st January 2007 and 31st December 2009.
13,112 US Medicare beneficiaries developed incident zoster; the overall zoster incidence rate was 10.0 (9.8–10.2) per 1,000 person-years in the unvaccinated group and 5.4 (95% CI 4.6–6.4) per 1,000 person-years in vaccinees, giving an adjusted VE against incident zoster of 0.48 (95% CI 0.39–0.56). In **immunocompromised vaccinees**, there were 24 events in 1,981 person-years of follow-up, giving an adjusted VE of 0.37 (95% CI 0.06–0.58).

Incidence rates for herpes zoster using the antiviral definition were higher in older age groups, in women, in those with any immunosuppression (adjusted hazard ratio 1.80 [95% CI 1.70–1.90]) and in those with specified immune-mediated disorders, including inflammatory bowel disease and SLE, and other disorders such as chronic kidney disease and COPD.

[Zhang 2012]

A retrospective cohort study of 463 541 Medicare beneficiaries 60 years and older with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease using Medicare claims data.
Median duration of follow-up was 2.0 years (interquartile range, 0.8-3.0); 4.0% of patients received HZ vaccine. The overall crude HZ incidence rate was 7.8 cases per 1000 person-years (95% CI, 3.7-16.5) within 42 days after vaccination. The rate among the unvaccinated was 11.6 cases per 1000 person-years (95% CI, 11.4- 11.9). Among 633 patients **exposed to biologics** at the time of vaccination or within the subsequent 42 days, no case of HZ or varicella occurred. After multivariable adjustment, HZ vaccination was associated with a hazard ratio of 0.61 (95% CI, 0.52- 0.71) for HZ risk after 42 days.
Receipt of HZ vaccine was not associated with a short-term increase in HZ incidence among Medicare beneficiaries with selected immune-mediated diseases, including those exposed to biologics.

[Tseng 2011]

The incidence of acute symptomatic indicator conditions was compared in the vaccinated and age-matched unvaccinated cohorts. The adjusted rate ratios for the 13 conditions ranged from 0.76 to 1.38 (mean 1.05; SD 0.19), being 1.0 or greater for 7 of the 13 conditions.

Discussion

According to the EMA, Zostavax can be administered concomitantly with inactivated influenza vaccine as separate injections and at different body sites. This is relevant because influenza vaccine is often given to elderly people (mostly 60-65 years old) as an annual vaccination. A disavantage of the study is the fact that the incidences of HZ and of PHN has not been studied in these patients.

23-valent pneumococcal polysaccharide vaccine should not be given together with Zostavax because concomitant use could reduce the immunogenicity of Zostavax.

According to the SPC, participants with a history of herpes zoster (HZ), VZV-seronegative or low seropositive persons are not contraindicated. ZOSTAVAX is also 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. A disavantage of the study is the fact that the incidences of HZ and of PHN has not been studied in these patients.

Immunosuppressive therapy (including high-dose corticosteroids), primary and acquired immunodeficiency states are denominated as a contraindication. The efficacy of ZOSTAVAX have not been established in adults with HIV/AIDS, the use of Zostavax is in this case also contraindicated.

The HZ vaccine is contraindicated in patients taking anti-tumor necrosis factor (anti-TNF) therapies or other biologics commonly used to treat immune-mediated diseases. A study [Zhang 2012] didn't find an increase in HZ incidence in those patients.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒ no information on hiv
No ☐

[D0011D]: What are the hospitalisation rates?

Methods

☐ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation (REA submission file, SPC and EPAR's of Zostavax by CHMP/EMA) ☒
- Domain search ☒
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review as referred above.

Method of synthesis: narrative

Result

[Oxman (2005)]

The number of participants who had one or more hospitalisations was similar in the two groups. No hospitalisation among participants in either group was considered to be related to the vaccine.

Table. Adverse Events among All Subjects and among Those in the Adverse-Events Substudy.*

	Vaccine group (zoster vaccine)	Placebo group	Difference in Risk (95% CI)
HOSPITALISATION			
No. of subjects	3345	3271	
Day of vaccination to end of study			
Subjects hospitalized	1137 (34.0%)	1115 (34.1%)	0.1 (-8.8 to 9.0)†
Hospitalisation related to herpes zoster	5 (0.2%)	6 (0.2%)	-0.1 (-0.7 to 0.5)†

** The rates of death and of hospitalisation are percentages of subjects in each treatment group. Otherwise, percentages are rates weighted in proportion to the number of subjects with safety follow-up in each age group. NC denotes not calculated. Three subjects who had withdrawn from the study because of worsening health and subsequently died were included in the safety analysis.*
† The difference in risk (vaccine group-placebo group) and the 95 percent confidence intervals for deaths [and hospitalisations] are based on the rates per 1000 subject-years of follow-up to account for differential follow-up among the study participants as a result of staggered enrollment. Otherwise, the differences in risk and 95 percent confidence intervals are based on an asymptotic method for the difference of two binomial proportions where the proportions are weighted according to the number of subjects with safety follow-up in each age group. Negative values for the difference in risk result when the rate in the placebo group is larger than that in the vaccine group.

Source: *Adapted from 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(22):2271-84.*

[Simberkoff (2010)]

Long-term follow-up (mean 3.39 years) showed that rates of hospitalisation ~~or death~~ did not differ between vaccine and placebo recipients.

See figure 2 in appendix

Table. Time to first hospitalisation for participants in the adverse events substudy.

Age group	Treatment group	Years of follow-up				
		0	1	2	3	4
60-69	Zostavax	1 724	1 584	1 438	1 284	683
	Placebo	1 729	1 548	1 410	1 276	656
70 years or more	Zostavax	1 612	1 387	1 189	1 006	489
	Placebo	1 541	1 349	1 177	973	513

Source: *Adapted from Simberkoff MS, Arbeit RD, Johnson GR, et al. Shingles Prevention Study Group. Safety of herpes zoster vaccine in the shingles prevention study:a randomized trial. Ann Intern Med 2010;152(9):545-54.*

[EMA/CHMP (2006)]

The rates of HZ-related hospitalisation in the zoster vaccine group (5 hospitalisations) and the placebo group (6 hospitalisations) were not different.

[FDA (2006)]

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

[Tsjeng 2011]

Real life data show that 10.1% of HZ vaccine recipients had at least one hospitalisation versus 12.8% in no vaccinated. HZ vaccine recipients had reduced risk of hospitalisation (HR, 0.35; 95% CI, 0.24-0.51).

Discussion

The rates of HZ-related hospitalisation in the zoster vaccine group and the placebo group were not different in the SPS study. In contrast, real life data from the USA seemed to show some effect of vaccination on the number of hospitalisations.

In the clinical trials, a higher age leads to a higher cumulative hospitalisation rate irrespective of the treatment. Although there might be some indication from real life

that there is a relation between vaccination with Zostavax and the number of hospitalisation at this moment there is insufficient evidence that this vaccine will decrease the number of hospitalisations due to zoster.

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

[D0011E]: Is a booster injection needed? If yes, when will that be needed and for whom?

Methods

☐ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation (REA submission file, SPC and EPAR's of Zostavax by CHMP/EMA) ☒
- Domain search ☒
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review as referred above.

Method of synthesis: narrative

Result

[EMA (2006)]

The company [SPMSD] agreed that there is a need to determine long-term duration of vaccine protection and committed to further assess the long-term efficacy through extension of follow-up of around 7000 vaccinated participants (from study 004) for up to 10 years post vaccination, in order to detect potential waning of protection.

Summary of the risk management plan (partly):

Safety issue Proposed pharmacovigilance	activities	Proposed risk minimisation activities
Unknown duration of Protection and need for a booster dose, with theoretical possibility to shift the occurrence of HZ to an older age.	Study of long-term persistence of efficacy (extension of Protocol 004 and Protocol 013 which extends follow-up through 10 years postvaccination for about 7000 recipients)	--

[The UK Joint Committee on Vaccination and Immunisation (JCVI), (2010)]

The duration of protection (i.e. 7.5 years) at time of assessment, with the objective not to vaccinate too early to make sure people 70+ (the ones who will benefit the most) are protected.

[SPMSD submission file (2013)]

Duration of vaccine protection

Long-term follow-up of vaccine efficacy (up to 10 years post-vaccination) has been conducted for a subgroup of participants≥60 years included in the first phase III efficacy pivotal study (SPS). No similar follow-up was planned for the second phase III efficacy pivotal study (ZEST) where participants aged 50 to 59 were followed up to 2 years.

A study –protocol 029 (see Appendix 5 of the submission file) – is on-going to evaluate the safety, tolerability and immunogenicity of ZOSTAVAX administered as a booster dose ≥10 years after a first dose (in 200 participants ≥70 years of age who received ZOSTAVAX in the SPS) versus a first dose in participants ≥70 years (age and gender matched) or in participants 60-69 or in participants 50-59. Full Clinical Study Report is expected in 2014 [clinical trial protocol, NCT01245751, study is closed].

Discussion

Vaccine efficacy persists for at least 7 years. A study of long-term persistence of efficacy for up to 10 years post vaccination is ongoing. It is not known whether a booster is needed and if so, when. There is also a lack of knowledge about the effectiveness of a second dose of vaccine.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

[D0016]: How does the use of Zostavax affect activities of daily living?

[D0012]: What is the effect of Zostavax on generic health-related quality of life?

[D0013]: What is the effect of Zostavax on disease-specific quality of life?

Methods

☐ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation (REA submission file, SPC and EPAR's of Zostavax by CHMP/EMA) ☒
- Domain search ☒
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review as referred above.

Method of synthesis: narrative

Methodology

In the study of Schmader (2010; SPS population), the efficacy of the zoster vaccine on herpes zoster (HR)-related interference with activities of daily living (ADLs) and health-related quality of life (HRQL) were determined.

HZ burden of interference with ADLs and HRQL using ratings from the Zoster Brief Pain Inventory (ZBPI) and Medical Outcomes Study 12-item Short Form Survey (SF-12) mental component summary (MCS) and physical component summary (PCS) scores were measured.

The ZBPI was used to quantify HZ pain and discomfort (including allodynia and pruritus) and measure selected ADLs and health. It uses an 11-point Likert scale (0–10) to rate HZ pain and discomfort for four dimensions (worst, least, average during the past 24 hours and now) and HZ pain and discomfort–related interference with seven ADL and health items: general activity, mood, walking ability, work, relations with others, sleep, and enjoyment of life.

It should be noted that the functional and health items in the ZBPI do not include several ADLs and measures of HRQL that are important to older people. The Zoster Impact Questionnaire (ZIQ) was developed to rectify this deficiency of validation in elderly people (≥ 60 year). According to the authors the data of ZIQ and ZBPI were similar, but these data were not shown.

Quantifications

ZBPI ADL Interference

For the purposes of this analysis, the ZBPI ADL interference items were summarized into a single score by taking the mean of the seven items, using an approach recommended previously.

ZBPI ADL Severity of Interference

For each evaluable case of HZ, the ZBPI interference data were used to calculate an ADL Severity of Interference score, defined as the area under the ZBPI interference summary score–versus-time curve (AUC) for the 182-day period for a single case of HZ.

Higher Severity of Interference scores indicated greater functional interference.

The ZBPI Severity of Interference score was defined as 0 for participants who did not develop an evaluable case of HZ during the study. A ZBPI ADL Severity of Interference score of 300 or greater was considered severe, because this threshold correlates with markedly poor quality of life and functional status.

The SF-12 MCS and PCS scores were employed in a similar fashion to determine a HRQL response-versus-time curve for the 182- day period for each evaluable case of HZ. Higher SF-12 scores indicate better HRQL.

ZBPI ADL Burden of Interference

The ZBPI ADL Burden of Interference score represents the average Severity of Interference score (severity of interference) of participants in the vaccine and placebo groups; it was calculated as the sum of the ZBPI ADL Severity of Interference scores of all members of a group divided by the total number of participant-years of follow-up in that group.

The observed ZBPI ADL Burden of Interference score was calculated as a weighted average stratified according to age group, with weights proportional to the total follow-up time in each age group. Similar calculations were performed with the SF-12 MSC and PSC scores to determine the average rating of HRQL of participants in the vaccine and placebo groups.

Health Related Quality of Life (HRQL)

No HZ-specific measure of HRQL was available for the study. Therefore, two generic measures of HRQL were chosen: the EuroQol visual analog scale **(VAS**) and the Medical Outcomes Study 12-item Short Form Survey (**SF-12**). The SF-12 includes ratings of general health, limitations in moderate activities, limitations in climbing several flights of stairs, accomplishing less than one would like as a result of physical health, limitations in kind of work or other activities as a result of physical health, accomplishing less than one would like as a result of emotional problems, not doing work or other activities as carefully as usual as a result of emotional problems, how much pain interfered with work, amount of time feeling calm and peaceful, amount of time having a lot of energy, amount of time feeling downhearted and blue, and how physical or emotional health has interfered with social activities.

The SF-12 has been validated for use in U.S. populations and is summarized into Mental and Physical Health Summary Scales, providing Mental Component Summary (**MCS**) and Physical Component Summary (**PCS**) scores. These summary scales are standardized to have a population mean of 50.

Vaccine Efficacy (VE)

Vaccine efficacy for ZBPI Burden of Interference was defined as the difference in ZBPI Burden of Interference between the vaccine and placebo groups. Vaccine efficacy for SF-12 MCS and PCS scores was defined as the difference in average area under the curve for the SF-12 MCS and PCS scores between the vaccine and placebo groups. For HRQL analyses, higher area under the curve indicates better HRQL.

Result

Activities of daily living (ADL)

[Schmader 2010].

Table. Zoster **Vaccine Efficacy** for Zoster Brief Pain Inventory (ZBPI) Activity of Daily Living (ADL) Burden of Interference According to Age in All Randomized Subjects (Modified-Intention-to-Treat Population).

	Zoster vaccine	Placebo	
	ZBPI ADL Burden of Interference Score*	ZBPI ADL Burden of Interference Score*	Vaccine Efficacy for ZBPI ADL Burden of Interference Point Estimate (95% CI)†
Age (years)			
All	0.89	2.64	66.2 (55.4–74.4)
60-64	0.52	1.95	73.1 (47.0–86.3)
65-69	0.71	2.18	67.4 (44.1–81.0)
70-74	1.16	2.96	60.8 (35.2–76.3)
75-79	1.38	3.66	62.3 (29.8–79.7
≥80	2.11	5.16	59.0 (11.0–81.1)

** ZBPI ADL Burden of Interference score is calculated as the sum of the ZBPI ADL Interference scores (the areas under the ZBPI ADL Interference score versus time curves during the 6-month period after herpes zoster (HZ) rash onset) for all subjects in the group divided by subject years of follow-up. Subjects who did not develop HZ during the study were assigned a ZBPI ADL Interference score of 0. The figure for all ages is the weighted average of the observed burden of interference of ZBPI ADL stratified according to age group, with weights proportional to the total follow-up time in each age group.*
† For all ages, the ZBPI ADL Burden of Interference is calculated as a weighted average of the observed vaccine efficacy stratified according to age group with weights proportional to the total follow-up time in each age group. The confidence interval (CI) is constructed based on the large sample approximation under the fixed number of events design.

Source: *Adapted from Schmader KE, Levin MJ, Gnann JW Jr, et al. Efficacy, Safety, and Tolerability of Herpes Zoster Vaccine in Persons Aged 50-59 Years. Clin Infect Dis 2012;54(7):922-8.*

[Schmader 2010]. Burden of Interference.

Table. Zoster vaccine efficacy for Zoster Brief Pain Inventory (ZBPI) Activity of Daily Living (ADL) Burden of Interference According to Age in Evaluable Cases of erpes Zoster (HZ).

Age group	Evaluable cases of HZ in the mITT population, n		ZBPI ADL Burden of Interference Score*		Zostavax efficacy for ZBPI Severity of Interference Point Estimate (95% CI)^
	Zostavax	Placebo	Zostavax	Placebo	
All	315	642	57.8	81.6	29.2 (7.0; 46.0)
60-64	54	153	50.7	66.2	23.4 (-50.8; 61.1)
65-69	68	181	53.8	62.0	13.3 (-48.6; 49.4)
70-74	89	158	59.2	85.3	30.6 (-14.7; 58.0)
75-79	67	103	63.4	106.6	40.5 (-10.7; 68.1)
≥80	37	47	72.1	146.1	50.7 (-7.2; 77.3)

**ZBPI ADL Burden of Interference score was calculated as the sum of the ZBPI ADL Interference scores (the areas under the ZBPI ADL Interference score versus time curves during the 6-month period after HZ rash onset) for all subjects in the group with HZ divided by the number of subjects in the group with HZ.*
^ZBPI ADL Burden of Intereference was calculated as a weighted average of the observed vaccine efficacy.

Source: *Adapted from Schmader KE, Levin MJ, Gnann JW Jr, et al. Efficacy, Safety, and Tolerability of Herpes Zoster Vaccine in Persons Aged 50-59 Years. Clin Infect Dis 2012;54(7):922-8.*

Schmader 2010

For the modified-intention-to-treat population, the overall zoster vaccine efficacy was 66% (95% confidence interval (CI) =55–74%) for ZBPI ADL burden of interference score and 55% (95% CI =48–61%) for both the SF-12 MCS and PCS scores. Of participants who

developed HZ, zoster vaccine reduced the ZBPI ADL burden of interference score by 31% (95% CI=12–51%) and did not significantly reduce the effect on HRQL.

Schmader 2010

Table. Zoster Vaccine efficacy in all participants (mITT) and in evaluable cases of HZ.

Analysis	HZ BOI score (95% CI) [%]	ZBPI BOI score (95% CI) [%]	SF-12 MCS score (95% CI) [%]	SF-12 PCS score (95% CI) [%]
mITT	61 (51; 69)	66 (55; 74)	55 (48; 61)	55 (48; 61)
In evaluable cases of HZ	19 (2; 35)	29 (7; 46)	5.2 (-9.4; 17.8)	3.9 (-11; 16)

Abbreviations: ***HZ BOI*** *(Herpes Zoster Pain and Discomfort Burden of Illness);* ***ZBPI BOI*** *(Zoster Brief Pain Inventory Activity of Daily Living Burden of Interference);* ***SF-12 MCS*** *(12-item Short Form Survey Mental Component Summary);* ***SF-12 PCS*** *(12-item Short Form Survey Physical Component Sumarry).*

Source: *Schmader KE, Johnson GR, Saddier P, Ciarleglio M, Wang WW, Zhang JH, et al. Effect of a zoster vaccine on herpes zoster-related interference with functional status and health-related quality-of-life measures in older adults. J Am Geriatr Soc 2010 Sep;58(9):1634-41.*

Schmader 2010

Zoster vaccine had only a minimal effect on the effect of HZ on HRQL, which was measured using generic instruments, including the EuroQol VAS and SF-12 (a 5–10% reduction, which was not statistically significant).

[Fried 2010]

Schmader and colleagues' article reports an originally planned analysis from the SPS. In brief, they report that in participants who developed HZ, vaccine modestly lessened (by circa 30%) the effect of HZ on daily functioning but not on HRQL. The authors (Schmader et al.) attribute this disparity to greater sensitivity of the daily functioning measures to the effect of HZ. The standard instruments used to measure HRQL did not specifically mention shingles and did not show a vaccine benefit in patients with HZ.

[Gagliardi 2012]

The interference of herpes zoster in activities of daily life (**ADL**) was measured by the zoster brief pain inventory (ZBPI ADL), in which scores greater than or equal to 300 indicate significant pain-related interference in daily life (VE for severe ADL interference) and quality of life. There were *no significant differences* between vaccinated and placebo groups for this outcome of severe ADL in the study by Oxman 2005 (RR 0.63, 95% CI 0.34 to 1.16) (Analysis 1.2).

Table. Comparison I Zoster vaccine versus placebo, Outcome 2 Herpes zoster cases with ZBPI ADL. Severity of Interferences scores of 300 or greater (high score is worse).

Study or subgroup	Vaccin n/N	Placebo n/N	Risk ratio M-H, Fixed, 95% CI
Oxman 2005	13/315	42/642	0.63 [0.34, 1.16]

Source: *Adapted from Gagliardi AMZ, Gomes Silva BN, Torloni MR, et al. Vaccines for preventing herpes zoster in older adults. Cochrane Database Syst Rev 2012:CD008858.*

According to a few observational studies (Katz 2004; Lydick 1995; Schmader 2007) acute herpes zoster pain can have an important negative impact on the lives of a significant proportion of affected individuals. However, one randomised study did not detect significant differences in the **health-related quality of life** of herpes zoster patients treated with placebo compared to analgesics (Dworkin 2009). Only one of the studies included in our review addressed this issue (Oxman 2005) *and did not detect significant differences* between the zoster vaccine versus the placebo groups. The advantage of the vaccine is that it reduces the risk of developing herpes zoster, a disease that can potentially affect the quality of life of affected individuals.

[EMA 2006]

Compared with placebo, zoster vaccine resulted in an 8.2% reduction in the risk of having substantial ADLI (defined as having a combined ADLI score ≥2 for ≥7 days) beyond the reduction in HZ. The hypothesis testing on this endpoint was not statistically significant (p-value=0.341).

Health Related Quality of Life (HRQL)

[Schmader 2010]

Vaccine Efficacy for All Participants

In the modified-intention-to-treat population, zoster vaccine reduced the effect on physical HRQL as measured using the SF-12 PCS score by 55% (95% CI=48–61%) and the effect on mental HRQL as measured using the SF-12 MCS score by 55% (95% CI=48–61%) (Figure 1). In the intention-to-treat population, zoster vaccine reduced the effect on physical HRQL as measured using the SF-12 PCS score by 56% (95% CI=48–62%) and the effect on mental HRQL as measured using the SF-12 MCS score by 56% (95% CI=49–62%). For comparison, vaccine efficacy for these parameters was slightly lower than vaccine efficacy for the HZ Pain and Discomfort Burden of Illness score and for the ZBPI ADL Burden of Interference score (Figure 1).

Vaccine Efficacy for Participants with HZ

In participants with HZ, zoster vaccine had minimal effects on the effect of HZ on HRQL measured using the SF-12 PCS score (vaccine efficacy 3.9%, 95% CI= -1.1–16%) and the SF-12 MCS score (vaccine efficacy 5.2%, 95% CI= -9.4–18%) (Figure 2). The results of the intention to- treat analyses were nearly identical for the SF-12 PCS (vaccine efficacy 3.9% (95% CI= -1.1–17%) and the SF-12 MCS (vaccine efficacy 5.1% (95% CI=9.4–18%). For comparison, these effects of zoster vaccine were less than the vaccine efficacy for the HZ Pain and Discomfort Burden of Illness score and for the ZBPI ADL Burden of Interference score (Figure 2).

Discussion

Schmader and Gagliardi both reported about the efficacy of the zoster vaccine on herpes zoster (HR)-related interference with activities of daily living (ADLs) and health-related quality of life (HRQL). Although both authors analysed data from the same population (SPS), different conclusions were drawn.

Schmader:

For the modified-intention-to-treat population, the overall zoster vaccine efficacy was 66% (95% confidence interval (CI) =55–74%) for ZBPI ADL burden of interference score and 55% (95% CI =48–61%) for both the SF-12 MCS and PCS scores. Of participants who developed HZ, zoster vaccine reduced the ZBPI ADL burden of interference score by 31% (95% CI:12–51%) and did not significantly reduce the effect on HRQL.

CONCLUSION of the authors: Zoster vaccine reduced the burden of HZ-related interference with ADLs in the population of vaccinees and in vaccinees who developed HZ. Zoster vaccine reduced the effect of HZ on HRQL in the population of vaccinees but not in vaccinees who developed HZ.

Gagliardi:

Only one of the studies included in the Cochrane review addressed this issue (health-related quality of life) and did not detect significant differences between the zoster vaccine versus the placebo groups. There were no significant differences between vaccinated and placebo groups for this outcome (ZBPI severe ADL) in the study by [Oxman 2005] (RR 0.63, 95% CI 0.34 to 1.16).

The lacking of all input data needed and the enormous complexity to calculate the ZBPI scores make a new calculation for this assessment not feasible. In patients who developed HZ, vaccine modestly seems to decrease (by circa 30% at the most) the effect of HZ on daily functioning but not on HRQL. This was not confirmed by [Gagliardi]. Data about disease specific quality of life were not available.

References

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2. European Medicine Agency. EPAR - Scientific Discussion Zostavax®, variation. Procedure no EMEA/H/C/674/II/3. London, 21/06/2007. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion_-_Variation/human/000674/WC500053464.pdf

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Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☐
Partly ☒
Not ☐

[D0017]: Was the use of Zostavax worthwhile? What is the effect of real life use of Zostavax?

Methods

☐ See general description of methods (Appendix 1)

☐ Other, please specify:

Source of information:

- Basic documentation (REA submission file, SPC and EPAR's of Zostavax by CHMP/EMA) ☒
- Domain search ☒
- Other: [use also Table 2 to document]

Critical appraisal criteria: No qualitative tool was used for the review as referred above.

Method of synthesis: narrative

Result

Table. Characteristics of retrospective HZ vaccination studies

	Tseng (2011)	Zhang (2012)	Langan (2013)
Type of patients (unvac:vac)	Immunocompetent community dwelling adults from Kaiser Permanente	Medicare beneficiaries with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis or inflammatory bowel disease	Medicare beneficiaries
Number of patients (unvac:vac)	(227.923:75.761)	463,541	766.330 (736.545;29,785)
Age distribution	60+	60+	65+
Which diagnoses	HZ and ophthalmic HZ	HZ	HZ and PHN
Definition (HZ, PNH)	ICD-9 code (HZ=0,53.xx and oHZ=0.53.2x)	ICD-9-CM code 053) in an inpatient or physician office visit claim that was accompanied by a pharmacy claim for antiviral treatment	ICD-9-CM code for HZ (not defined), no ICD-9-CM codes for PHN, and the use of antivirals (acyclovir, famciclover or valciclovir) 7 days before or after the

	Tseng (2011)	Zhang (2012)	Langan (2013)
		(aciclovir, famciclovir, valaciclovir) within 7 days before or after the diagnosis.	diagnosis; First episode of HZ with a further HZ diagnostic code after 90 days with a relevant prescription for analgesic, anticonvulsant or antidepressant on the same day as the recorded consultation
Follow-up (unvac:vac)	(1,56:1,72)	2.0	1,72
Time horizon	01/01/2007 – 31/12/2009	01/01-2006 – 31/12/2009	01/01/2007 – 31/12/2009
Additional notes		Underlying disease is defined on a number of criteria. For more details see manuscript.	

unvac=unvaccinated, vac=vaccinated,

Three retrospective studies about real life use of Zostavax are published (see table 1). The studies of Tseng (2011) and of Langan (2013) are random selections of beneficiaries (from Kaiser Permanente respectively Medicare). The study of Zhang (2012; beneficiaries of Medicare) is selected on patients with immune-mediated diseases (see table 1). For having immunosuppressive therapy (including high-dose of corticosteroids) is a contraindication for Zostavax and therefore excluded from participating in the RCT's, little information is known about this group.

[Tseng 2011]

A retrospective cohort study from 01-01-2007 through 31-12-2009, of individuals enrolled in the Kaiser Permanente Southern California health plan. Participants were **immunocompetent** community-dwelling adults aged 60 years or older. The 75,761 members in the vaccinated cohort were age matched (1:3) to 227,283 unvaccinated members. Follow-up periods are on average 1.56 years (unvaccinated cohort) and 1.72 years (vaccinated cohort).

Incident herpes zoster and ophthalmic herpes zoster were defined by *International Classification of Diseases, Ninth Revision (ICD-9)* codes (053.XX and 053.2X, respectively; in any position) from hospital, outpatient, and emergency department settings during the study period. According to the paper of Zhang the positive predictive value of using to HZ diagnosis alone is between 85% and 100%.

Results

Among unvaccinated individuals, herpes zoster incidence varied by several factors. It increased with age (≥80 years versus 60-64 years: HR 1.45; 95% CI:1.30-1.63; subgroup of ≥80 years old HR: 0.44 (95% CI: 0.35-0.56), was lower in men and in black individuals. It varied by chronic disease, being higher in individuals with lung disease as compared with those without. In addition, the risk of herpes zoster was associated with number of outpatient visits during the year before the index dates, an indicator of health care–seeking behaviour. There was no association between hospitalisations or emergency department visits and herpes zoster.

The number of herpes zoster cases among vaccinated individuals was 828 in 130,415 person-years (6.4 per 1000 person-years; 95% confidence interval [CI], 5.9-6.8), and for unvaccinated individuals it was 4,606 in 355,659 person-years (13.0 per 1000 person-years; 95% CI: 12.6-13.3). In adjusted analysis, vaccination was associated with a reduced risk of herpes zoster (hazard ratio [HR] 0.45; 95% CI: 0.42-0.48). Vaccine efficacy (1 minus the hazard ration) can be calculated as 0.55.

In the manuscript it was also reported that ophthalmic herpes zoster (HR, 0.37; 95% CI, 0.23-0.61) and hospitalisations coded as herpes zoster (HR, 0.35; 95% CI, 0.24-0.51) were less likely among vaccine recipients. Detailed information about the incidences of ophthalmic HZ or the hospitalisation rates was lacking in the article.

[Langan 2013]

A cohort study of 766,330 Medicare beneficiaries (which is a 5% random sample of Medicare) of ≥65 years were studied. During the study period from 01-01-2007 through 31-12-2009, 29,785 participants (3,9% of the cohort; 2,1% of person times) had received a herpes zoster vaccine. Immunosuppression was identified in case of leukemia, lymphoma, or HIV (as determined by the presence of two diagnostic ICD-9-CM codes on different days within outpatient, inpatient, or provider files). Other comorbidities previously identified as being associated with increased risks of zoster are chronic obstructive pulmonary disease (COPD), diabetes, and systemic lupus erythematosis (SLE). Individuals with autoimmune disorders such as SLE were considered immunocompetent unless they received immunosuppressive therapy.

Within the cohort, 140,925 individuals were immunosuppressed at some point during follow-up and 4,469 of these individuals were immunosuppressed at the time of herpes zoster vaccination.

HZ cases are identified using administrative sources: ICD-9-CM code for HZ (not specifically mentioned), no ICD-9-CM codes for PHN, and the use of antivirals (acyclovir, famciclover or valciclovir) 7 days before or after the diagnosis. Actually, two definitions for HZ were used in this manuscript; one with additional antiviral therapy and one without additional antiviral therapy. PHN was identified as those with a first episode of zoster with a further zoster diagnostic code after 90 days with a relevant prescription for analgesic, anticonvulsant or antidepressant therapy on the same day as the recorded consultation. Vaccine effectiveness (VE) was calculated as (1 – the adjusted hazard ratio).

Results:

Incidence rates for herpes zoster using the antiviral definition were higher in older age groups, in women, in those with any immunosuppression (adjusted hazard ratio 1.80 [95% CI 1.70–1.90]) and in those with specified immune-mediated disorders, including inflammatory bowel disease and SLE, and other disorders such as chronic kidney disease and COPD (Table 2 of Langan, that part of the table was not shown). Lower incidence rates were seen in people who reported being black (adjusted hazard ratio 0.51 ([95% CI 0.47–0.56]) and those with any evidence of low income (adjusted hazard ratio 0.86 [95% CI 0.82–0.90]).

Overall, 154 vaccinees experienced an incident of herpes zoster episode (defined using the specific antiviral definition) during 28,291 person-years of follow-up compared to 12,958 events in 1,291,829 person-years of follow-up in those not vaccinated, giving an incidence rate of herpes zoster in vaccinees of 5.4 (95% CI: 4.6– 6.4) per 1,000 person-years compared to 10.0 (95% CI: 9.8–10.2) per 1,000 person-years in those not vaccinated. The adj. HR for vaccination is 0.52 (95% CI: 0.44-0.61) for overall. For the immunocompetent subgroup is that 0.49 (0.41-0.59) and for the immunosuppressed subgroup 0.63 (0.42-0.94).

The overall vaccine effectiveness (VE) for herpes zoster in vaccinees adjusted for age, gender, race, immunosuppression, low income, and comorbidity was 0.48 (95% CI 0.39–0.56). In the subgroup of immunosuppressed individuals, VE against zoster was 0.37 (95% CI: 0.06-0.58). Using the definition for HZ without antiviral therapy, the effect of vaccination on the incidence of HZ was less pronounced.At 90 days or greater following zoster, the adj. Hazard Ratio of vaccination for PHN was 0.41 (95% CI: 0.21-0.79). VE against PHN after adjusting for patient characteristics and comorbidities was calculated as 0.59 (95% CI: 0.21-0.79). In patients with HZ the adjusted VE against PNH was calculated 0.64 (95% CI: 0.11-0.85). Lower VE aginst PNH were also demonstrated using the definition without antiviral therapy.[Zhang 2012]

To examine the association between HZ vaccination and HZ incidence in selected immune-mediated diseases in real life situation, a retrospective cohort study has been performed among Medicare (US) beneficiaries.

463,541 individuals of 60 years and older with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis or inflammatory bowel disease were studied using Medicare claims data from 01-01-2006 through 31-12-2009. Mean duration of follow-up was 2.0 years (interquartile range 0.8-3.0); mean age (SD) at the start of the follow up

was 78 (8) years. 4% of the included participants received HZ vaccine. HZ cases were identified by the HZ diagnosis code (ICD-9-CM code 053) in an inpatient or physician office visit claim that was accompanied by a pharmacy claim for antiviral treatment (aciclovir, famciclovir, valaciclovir) within 7 days before or after the diagnosis.

Results:

The **incidence rate of HZ** (>42 days post vaccination) among the vaccinated was 6.7 cases per 1000 person-years (95% CI: 5.7-7.9) and among the unvaccinated 11.6 cases per 1000 person-years (95% CI: 11.4-11.9).

After multivariable adjustment, HZ vaccination was associated with a hazard ratio of 0.61 (95% CI: 0.52-0.71) for HZ risk after 42 days. Vaccine efficacy (1 minus the hazard ration) can be calculated as 0.39 (95% CI 0.39-0.48).Among unvaccinated persons, the HZ incidence rate differed by exposure to medications commonly used by patients with **immune-mediated diseases**. Exposure to oral glucocorticoids was associated with an 1.2 to 2.0 fold greater risk of HZ; the increase was significant for nearly all medication groups.

Based on the presented HZ incident rate (IR), a rate ratio can be calculated: 0.53 for biologicals (8.5/16.0), regardless of concomitant DMARDs or oral glucocorticoids; 0.53 for anti-TNF therapies (8.5/15.9); 0.51 for DMARDs, without biologicals but regardless of oral glucocorticoids (7.0/13.6); and 0.60 for oral glucocorticoids alone (10.3/17.2). As compared to the overall rate ratio (0.58; 6.7/11.6) the incidence rates were not significant different. In this retrospective study, the increased risk for HZ (1.2-2.0 fold) due to the studied immune-mediated disease was not further enlarged by vaccination.

Discussion

The efficacy of Zostavax to prevent herpes zoster in elderly people in a real life situation has been investigated in three retrospective cohort studies. [Langan 2013] focused on people ≥65 years old, while [Zhang 2012] and [Tseng 2011] on people ≥60 years old. All of them are retrospective cohort studies conducted in real clinical practice, therefore in case of their comparison with RCT, some methodological issues could emerge.
The three studies identified patients on the base of ICD 9 codes and prescribed antiviral therapies. All of them investigated incidence of HZ and vaccine efficacy.

In this study of [Tseng 2011] vaccination was associated with a reduced risk of herpes zoster (hazard ratio [HR] 0.45; 95% CI: 0.42-0.48), with a **VE HZ** of **0.55.** While in [Zhang 2012] VE HZ is in this case **0.39** (95% CI 0.39-0.48). The lower VE may be caused by the selected population (not only immune competent individuals).
In the study of [Langan 2013], the overall vaccine effectiveness (VE) for herpes zoster in vaccinees adjusted for age, gender, race, immunosuppression, low income, and comorbidity was **0.48** (95% CI 0.39–0.56). In the subgroup of immunosuppressed individuals, VE against zoster was 0.37 (95% CI: 0.06-0.58). [Langan 2013]. The studies of Zhang and Langan also seem to indicate that the VE of Zostavax against HZ seem to be less pronounced in the patients only identified on the basis of the ICD9 code for HZ than in patients who also receive antiviral therapy.

The incidence rates for herpes zoster were higher in older age groups, in women, and in immunocompromised persons [Langan 2013]. Among unvaccinated immunocompetent individuals, herpes zoster incidence increased with age (≥80 years versus 60-64 years: HR 1.45; 95% CI:1.30-1.63; subgroup of ≥80 years old HR: 0.44 (95% CI: 0.35-0.56), in the presence of lung disease and was lower in men and in black individuals [Tseng 2011]. Exposure to oral glucocorticoids (due to immune-mediated diseases) was associated with an 1.2 to 2.0 fold greater risk of HZ occurrence; vaccination did not enlarge this risk significantly in that study [Zhang 2012].

Vaccine efficacy against PHN was reported in the study of Langan. After adjusting for patient characteristics and comorbidities the **VE PHN** was calculated as **0.59** (95% CI: 0.21-0.79) [Langan].

In the retrospective study of Tseng 2011], herpes zoster vaccine recipients had reduced risks of ophthalmic herpes zoster (HR 0.37; 95% CI: 0.23-0.61) and hospitalisations coded as herpes zoster (HR 0.35; 95% CI: 0.24-0.51) [Tseng].

A decrease in ophalmic HZ after Zostavax has not reported before. This finding was also not observed in the SPS. However, due to lack of detailed information, it is difficult give a full interpretion for this single finding. Moreover, a reduced risk of hospitalisations due to Zostavax can not be confirmed by other studies, including the RCT's. Whether it is solely related to the effect upon ophalmic HZ remains unsolved.

The finding in RCT's that Zostavax is able to prevent HZ has been confirmed in the real life studies, although the effect seems somewhat less pronounced than in the setting of a clinical trial.

References

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2. Sanofi Pasteur MSD France. Marketing Authorization Holder submission file for shingles (herpes zoster) vaccine (live) Zostavax®. Submission date 12-04-2013.
3. Tseng HF, Smith N, Harpaz R, et al. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. JAMA.2011 Jan 12;305(2):160-6
4. Zhang J, Xie F, Delzell E, et al. 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.

Importance and transferability

How important is this piece of information for decision making?

Critical ☐
Important ☒
Optional ☐

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely ☒
Partly ☐
Not ☐

APPENDIX 3. CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS

1. Ethical	
1.1. Does the introduction of the new medicine and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
1.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be ethically relevant?	No
2. Organisational	
2.1. Does the introduction of the new medicine and its potential use/nonuse instead of the defined, existing comparators require organisational changes?	No
2.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be organisationally relevant?	No
3. **Social**:	
3.1. Does the introduction of the new medicine and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be socially relevant?	No
4. **Legal**:	
4.1. Does the introduction of the new medicine and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be legally relevant?	No

APPENDIX 4. ZOSTAVAX -CLINICAL DEVELOPMENT.

Table 1 of the submission file. ZOSTAVAX Clinical Development Plan – Pre-licensure

Protocol Number Study type Publication	Time	Study Title	Study population Intervention (N=) Comparator (N=)	Patient population	Length of Follow-up	Focus	Primary Safety Endpoints	Primary Efficacy Endpoints
P-001 (phase I) *Levin MJ et al, 2005**	1996-1998 US	Pilot Dose-Ranging Study to Assess the Safety and Tolerability of Live, Attenuated (Oka/Merck) Varicella-Zoster Vaccine in Healthy, Seropositive Adults 60 Years of Age and Older Frozen	Total N: 276; Vaccine Lots 1-6 : N= 41, 37, 42, 39, 41, 41 (6 potency levels) Placebo N= 35.	Healthy, VZV seropositive adults ≥60y Age range: 60-92 years	42 days	Safety and Dose-Ranging	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Immunogenicity only (antibody and CMI)
P-002 (phase IIb) *Schmader KE et al, 2006** [12]	1998-2004 US	Dose-Selection Study Using Live Attenuated (Oka/Merck) Varicella-Zoster Vaccine in Healthy Adults and in Adults with Diabetes Mellitus or Chronic Obstructive Pulmonary Disease 60 Years of Age and Older With a History of Varicella Frozen	Total N: 359; Low Potency N = 171, High Potency N = 171 Placebo: N = 56	Healthy Adults and Adults with Diabetes Mellitus or Chronic Obstructive Pulmonary Disease > 60 Years of Age with a History of Varicella Age range: 59-89 years.	42 days	Safety and Dose-Selection	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Immunogenicity only (antibody and CMI)
P-003 (phase IIb) Macaladad N et al, 2007(229)	1998-1999 US	Probe Study to Evaluation the Safety and Tolerability of High-Potency, Reformulated, Live, Attenuated Oka/Merck Varicella-Zoster Vaccine in Healthy Adults 30 Years of Age and Older, multicentre Study Frozen	Total N: 26; Vaccine N = 18, Placebo N = 3	Healthy Adults >30 Years of Age Low or undetectable VZV antibody titer at baseline Age range: 27-69 years	42 days	Safety	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Immunogenicity only (antibody)

[12] ** No full publication – Levin et al, 2005: poster presented at : 99th Annual Scientific Assembly of the Southern Medical Association November 10-13, 2005; Schmader et al, 2006: Geriatrics Society Annual Meeting May 3-7, 2006 Chicago, IL*

Protocol Number Study type Publication	Time	Study Title	Study population Intervention (N=) Comparator (N=)	Patient population	Length of Follow-up	Focus	Primary Safety Endpoints	Primary Efficacy Endpoints
P-004-08 *No publication*	2004 US	Safety study vaccinating placebo recipients previously enrolled in the SPS Frozen	Vaccine only; N = 13,681	Healthy, VZV seropositive adults >60y	NA	Safety, Tolerability	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	None
P-005 (phase IIb) *Levin MJ et al. 2003(240)* *Smith JG et al. 2003(241)*	1999-2000 US	Probe Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Process Upgrade Varicella-Zoster Vaccine as a Booster Dose in Previously Vaccinated Adults 60 Years of Age and Older Frozen	Vaccine only; N = 196	Healthy adults >60 Years of Age Subjects who had already received a VZV vaccine (live attenuated vaccine (N=155) or an inactivated vaccine (N=41)) > 5 years before Age range: 61-89 years	2 years	Safety, Tolerability, Immunogenicity	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Immunogenicity only (antibody)
• P-006 *Tyring S et al, 2012(242)*	2000-2003 US	Cell-Mediated Immune (CMI) response and zoster-associated pain in HZ patients Frozen	Total N = 280; No vaccine	Healthy adults >60y, who had not had HZ and which did not receive VZV vaccine before	10 days	Immunogenicity	None	Immunogenicity (CMI)
• P-007 (phase IIa) *Vermeulen JN et al. 2011(243)*	2001-2003 US	A Double-Blind, Randomized, Controlled, Multicenter Study to Evaluate the Safety, Tolerability and Immunogenicity After 1 and 2 Doses of Zoster Vaccine Frozen	Total N = 210; Vaccine N = 105, Placebo N = 105	Healthy adults .>60y Age range: 58-90 years	84 days	Safety, Tolerability, Immunogenicity	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Immunogenicity Parameters Only
P-009 (phase III) *Tyring SK et al, 2007(244)*	2003-2004 US	Evaluation of the Safety and Tolerability of a Higher Potency Dose of Varicella Zoster Virus Vaccine Live (Oka/Merck) Among Adults 50 Years of Age and Older	Total N = 695; Higher Potency Vaccine N = 461, Lower Potency Vaccine N =	Healthy adults >50y Age range: 50-90 years	42 days	Safety and Tolerability of Higher Potency Dose	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	None

Protocol Number Study type Publication	Time	Study Title	Study population Intervention (N=) Comparator (N=)	Patient population	Length of Follow-up	Focus	Primary Safety Endpoints	Primary Efficacy Endpoints
		Frozen	234					
P-010 (phase III) *Gilderman LI et al, 2008(224)*	2005 US	A Double-Blind, Randomized, Controlled, Multicenter Study to Evaluate the Safety, Tolerability and Immunogenicity of a Refrigerator-Stable Formulation of Zoster Vaccine Live (Oka/Merck)	Total N = 368; ZOSTAVAX refrigerated with PGSU N = 183, ZOSTAVAX frozen with PGS N = 185	Healthy adults >50y Age range: 50-99 years	28 days	Safety, tolerability and immunogenicity of Refrigerator-Stable Formulation	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Immunogenicity Parameters Only
P-011 (phase III) *Kerzner B et al, 2007(225)* • *Sutradhar SC et al, 2009(226)(meta-analysis P010 & P011)*	2005-2006 US	A Double-Blind, Randomized, Controlled, Multicenter Study to Evaluate the Safety, Tolerability and Immunogenicity of ZOSTAVAX administered concomitantly versus non concomitantly with influenza virus vaccine (inactivated) Frozen	Total N = 763; Concomitant group: N= 382, Non concomitant group: N = 381	Healthy adults >50 years Age range: 50-99 years	28 days	Safety, tolerability and immunogenicity during concomitant administration	All Adverse Experiences	Safety and Immunogenicity Parameters only

Source: *Adapted from Sanofi Pasteur MSD France. Marketing Authorization Holder submission file for shingles (herpes zoster) vaccine (live) Zostavax®. Submission date 12-04-2013.*

Table 2. ZOSTAVAX Clinical Development Plan- Post-licensure

Protocol Number Study type Publication	Time	Study Title	Study population Intervention (N=) Comparator (N=)	Patient population	Length of Follow-up	Focus	Primary Safety Endpoints	Primary Efficacy Endpoints
P-012 (phase III) RMP *MacIntyre CR at al, 2010(230)*	2000-2002 Germany, UK, Italy, Spain Australia Canada	Safety, Tolerability, and Immunogenicity of ZOSTAVAX Administered Concomitantly Versus Non-Concomitantly With PNEUMOVAX 23 in Subjects 60 Years of Age and Older. Refrigerated 4˚C	Total N = 473; Concomitant group: N= 237, Non concomitant group: n = 236	Healthy adults >60 Years of Age with no history of invasive pneumococcal disease or HZ	28 days	Safety, tolerability and immunogenicity	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Immunogenicity only (Antibody)
P-013 (phase III) FUM + RMP *No publication - SmPC(122)* [13]	2006-2011 US	Long-Term Persistence Study (LTPS) Persistence of zoster vaccine efficacy up to 10 years post-vaccination Frozen	Subgroup of subjects previously enrolled in the P-004 & P-004-05 (who had not developed HZ) Only subjects vaccinated with Zostavax. N=6 687 No placebo comparator – Use of historical controls to estimate vaccine efficacy	Healthy, VZV seropositive adults >60y from the P-004-5 (STPS) Mean age at enrolment in the LTPS = 74.5 years	Median 3.9 years [1 week to 4.75 years]	Efficacy persistence through year 10 post-vaccination	None	Efficacy: Herpes Zoster Pain Burden of Illness, Incidence of PHN, Incidence of HZ

[13] FUM: Follow-up Measure; RMP: Risk Management Plan

Protocol Number Study type Publication	Time	Study Title	Study population Intervention (N=) Comparator (N=)	Patient population	Length of Follow-up	Focus	Primary Safety Endpoints	Primary Efficacy Endpoints
P-014 (phase III) FUM + RMP *Mills R et al, 2010(227)*	2006-2007 US	Safety, Tolerability and Immunogenicity of Zoster Vaccine Live (Oka/Merck) in Subjects With a History of Herpes Zoster. Frozen	Stratified by number of years since HZ (5-9 years and ≥10 years, 2:1 ratio Total N= 101 Group 1 :N=51 Zostavax D1 and placebo 4 wks after ; Group 2 : N=50 placebo D1 and zostavax 4 wks after	Healthy adults >50 years of age with a history of HZ ≥5 years prior to enrolment (1 prior episode) Mean age at enrolment= 68.3 years for Group 1 and 67.4 years for Group 2.	8 weeks	Safety, tolerability and immunogenicity	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Immunogenicity only (Antibody)
P-016 (phase II) FUM + RMP *Benson CA, et al, 2012* [14]*	2009-ongoing (VZV-CMI analyses) US	Safety, tolerability, and immunogenicity of 2 doses of Zostavax in HIV-1-infected adults virologically suppressed on potent combination antiretroviral therapy (ART) Frozen	Total N = 395, stratified by screening CD4 (>350 copies/iL [H-CD4] versus ≥200 to 349 copies/iL [L-CD4]),	HIV infected adults .>18 with conserve immune function (CD4+ T cell count ≥200 cells/mL)	6 weeks after each vaccination	Safety, tolerability, and immunogenicity	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Immunogenicity only (Antibody)

[14] * Parrino et al. Poster presented at congress American College of Rheumatology 2011-no publication to date; Benson et al. CROI 2012. Abstract 96.FUM: Follow-up Measure; RMP: Risk Management Plan

Protocol Number Study type Publication	Time	Study Title	Study population Intervention (N=) Comparator (N=)	Patient population	Length of Follow-up	Focus	Primary Safety Endpoints	Primary Efficacy Endpoints
			- H-CD4 N= 203: 152 Zostavax & 51 placebo) - L-CD4 patients N= 192: 144 Zostavax & 48 placebo					
P-017 (phase III) FUM + RMP *Parrino J et al, 2011* - SmPC(122)*	2010 Germany, UK, France, Belgium	Safety, Tolerability and Immunogenicity of Zoster Vaccine Live (Oka/Merck) in Patients on Chronic/Maintenance Doses of Corticosteroids. Frozen	N= 309 2:1 ratio to receive either zoster vaccine or placebo stratified by prevaccination corticosteroid dose (5 to 10 mg; >10 to 20 mg)	Adults >60 years in chronic/maintenance systemic corticosteroid therapy: daily dose of 5 to 20 mg of prednisone or equivalent 2 weeks prior the enrolment and for the 6-week primary safety follow-up period	6 weeks	Safety, tolerability, and immunogenicity	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Immunogenicity only (Antibody)
P-019 (phase III) *No* publication	2007 Taiwan	Study the Safety, Tolerability, and Immunogenicity of ZOSTAVAX ® in Healthy Adults in Taiwan. Local registration Trial	N=150 Open label (no placebo)	Healthy adults >50 years	4 weeks	Safety, tolerability, and immunogenicity	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Immunogenicity only (Antibody)
P-020 (phase IV) RMP *Murray AV et al, 2011(210)*	2007-2009 Germany, UK, Spain, Netherlands, Canada	Safety and Tolerability of ZOSTAVAX™ in Subjects 60 Years of Age or Older. General safety study Refrigerated 4˚C	Total = 11,980 N=5,983 received Zostavax N=5,997 received	Healthy adults >60 years	182 days	Safety Severe Adverse Events (SAE)	Proportion of subjects reporting one or more SAEs within 42 d postvaccination and the secondary safety endpoint was the proportion of subjects reporting one or more SAEs within 182 d	None

Protocol Number Study type Publication	Time	Study Title	Study population Intervention (N=) Comparator (N=)	Patient population	Length of Follow-up	Focus	Primary Safety Endpoints	Primary Efficacy Endpoints
			placebo				postvaccination.	
P-021 (phase IV) RMP *Baxter R et al, 2012(211)*	2006-2007 US	Large scale observational post-licensure safety study Retrospective observational cohort study. Frozen	Total = 29,010 vaccinated with Zostavax. Subpopulations of interest: People ≥80 years of age, Diabetes, CHD, COPD, RA and immunocompromised also listed but too small.	Healthy adults >60 years, members of Kaiser Permanente Northern California (KPNC)	42 days	Safety Observational large-scale	Clinical events resulting in hospitalisations or emergency department visits in a 42-day risk time period immediately following vaccination - Review by an independent Safety Review Committee	None
P-022 (phase III) FUM + RMP *Schmader KE et al, 2012(207)*	2007-2010 Germany, Finland, Belgium, Canada	Efficacy, Safety, and Tolerability of Herpes Zoster Vaccine in Persons Aged 50–59 Years (ZEST) Frozen	Total = 22,439 Vaccine, N=11,211; Placebo, N= 11,228	Healthy adults 50-59 years, VZV seropositive, no history of HZ	Median 1.3 years [0 to 2 years]	Pivotal efficacy & safety (Phase III)	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Efficacy: Incidence of HZ, HZ related BOI (at 21 days) Immunogenicity (antibody)
P-024 FUM	On-going Until 2024 US	Long-term observational effectiveness study in the USA Frozen	Total = 30,000 (Target) Analysis in subpopulations: by Age (50-59, 60-69, ≥70) at vaccination & by time since vaccination	Healthy adults >50 years members of Kaiser Permanente Northern California (KPNC)	10 years	Real-life effectiveness – long term	None	Incidence of HZ in Vaccinated and Unvaccinated Cohorts, Incidence of Severe HZ including PHN in Vaccinated and Unvaccinated Cohorts
JV-1 X06Z305	2007-2009	Immunogenicity and Safety of a 1-Dose Regimen and	Total = 759 subjects:	Healthy adults >70	12	Immunogenicit	Adverse Events: Serious, Injection-Site, Systemic,	Immunogenicity (antibody at 4

Protocol Number Study type Publication	Time	Study Title	Study population Intervention (N=) Comparator (N=)	Patient population	Length of Follow-up	Focus	Primary Safety Endpoints	Primary Efficacy Endpoints
(phase III) FUM *Vesikari T et al, 2013(233)*	Finland, Germany, Italy, Spain, The Netherlands	Different 2-Dose Regimens of a Zoster Vaccine (Live), ZOSTAVAX ®, in Subjects ≥70 Years of Age. Refrigerated 4˚C	Group 1: vaccine at day 0 only (N=253), Group 2: vaccine at day0 + month 1 (N=255), Group 3: vaccine at day 0 + month 3 (N=251)	years (2/3 70-79 and 1/3 > 80 years)	months	y and safety	Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	weeks and at 1 year)
JV-2 FUM			3-lot comparison between refrigerated (4˚C) and frozen			Cancelled following CHMP conclusions (Nov.2010) based on integrated immunogenicity analysis		
JV-3 ZTV02C (phase IV) FUM *Arnou R et al, 2011(245)*	2008 France	Immunogenicity and safety of ZOSTAVAX® at minimum release specification approaching expiry potency in subjects ≥50 years old. Refrigerated 4˚C	Total = 96 No placebo – open label	Adults aged ≥50 years having a positive history of varicella (or residence for >30 years in a country with endemic VZV infection)	4 weeks	Immunogenicity and safety	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Immunogenicity (antibody pre-post-vaccination)
JV-4 ZTV03C (Phase III)	2001-Ongoing (immunogenicity analyses) CSR: Q4 2013 Spain, Germany	open-label, randomised, comparative, multicentre study of the immunogenicity and safety of ZOSTAVAX® when administered by intramuscular route or subcutaneous route to subjects at least 50 years of age	Zostavax administered by IM (Group 1) or SC route (Group 2)	Adults aged ≥50 years having a positive history of varicella (or residence for >30 years in a country with endemic VZV infection)	4 weeks	Immunogenicity and safety	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Immunogenicity (antibody pre-post-vaccination)
P-029 RMP	On-going; CSR: Q2 2014	Safety & Immunogenicity after a booster dose administered □10y following the initial dose (versus a 1st	N~600 Group 1: Booster Dose in ≥70 years	Adults aged ≥50 years (see groups for details), HZ history-negative	4 weeks	Immunogenicity and safety	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse	Immunogenicity (antibody and CMI)

Protocol Number Study type Publication	Time	Study Title	Study population Intervention (N=) Comparator (N=)	Patient population	Length of Follow-up	Focus	Primary Safety Endpoints	Primary Efficacy Endpoints
	US	dose of ZOSTAVAX) Frozen	who received ZOSTAVAX™ ~10 years before And 3 groups who never received Zostavax Group 2: 1st dose in ≥70years (matched with group 1) Group 3: 1st dose 60-69 Group 3: 1st dose 50-59	Group 1 being subjects from the SPS (P-004)			Experiences, Laboratory Parameters, Vital Signs	
P-042 (phase III) FUM	On-going; CSR: Q2 2013 US	Safety and Immunogenicity of ZOSTAVAX made with an alternative manufacturing process Refrigerated 4˚C	N~495 Zostavax new process Versus current process	Healthy adults aged ≥50 years	6 months	Immunogenicity and safety	Adverse Events: Serious, Injection-Site, Systemic, Elevated Temperature, Clinical Adverse Experiences, Laboratory Parameters, Vital Signs	Immunogenicity (antibody and CMI)

Source: *Adapted from Sanofi Pasteur MSD France. Marketing Authorization Holder submission file for shingles (herpes zoster) vaccine (live) Zostavax®. Submission date 12-04-2013.*

Table 3. ZOSTAVAX - additional studies - Merck or SPMSD: sponsor/collaborator/or not involved

Protocol Number Study type	Study Title	Study population Intervention (N=) Comparator (N=)	Patient population	Focus	Sponsor / Collaborator
P-051 AM2 NCT01385566 (Phase I) On-going http://ClinicalTrials.gov/show/NCT01385566	A Partially Blinded Randomized Clinical Trial to Study the Immunogenicity and Safety of Intradermal Administration of ZOSTAVAX™ (V211)	Zostavax administered by Intradermal (ID) or SC route at various doses N = 223	Healthy adults aged ≥50 years	Immunogenicity and safety	Merck
NCT01573182 (Phase II) *On-going* http://ClinicalTrials.gov/show/NCT00231816	Bone Marrow Transplant Donors: Vaccination of Stem Cell Donors With Zostavax to Reduce the Incidence of Herpes Zoster in Transplant Recipients - A Pilot Study The clinical hypotheses is: 1) that Zostavax given to stem cell donors will induce protective VZV specific T cell proliferation in allogeneic stem cell transplant recipients that can be transferred to recipients; 2) and that donor vaccination with Zostavax is safe for transplant recipients as measured by viral load measurement by PCR at the time of stem cell donation.	Zostavax administered by IM route N=40	VZV seropositive donors aged ≥50 years vaccinated 4 to 6 weeks prior to stem cell harvesting Aparied with allogeneic HSCT recipient	Immunogenicity and safety	**Sponsor:** University of Sydney **Collaborators:** - South West Sydney Local Health District -Merck
NCT00689013 Completed http://ClinicalTrials.gov/show/NCT00689013	The Effect of Pharmacist Intervention on the Use of Zostavax in a Community Pharmacy Setting	N=205	Adults aged ≥60 years		**Sponsor:** University of Tennessee **Collaborators:** - Merck - American Pharmacists

Protocol Number Study type	Study Title	Study population Intervention (N=) Comparator (N=)	Patient population	Focus	Sponsor / Collaborator
					Association
NCT01328548 (Observational) *On-going* http://ClinicalTrials.gov/show/NCT01328548	Zoster Vaccine Response in the Frail Elderly	N=250	Elderly, non-ambulatory residents of nursing homes (80 years or older).	Immunogenicity	**Sponsor:** McMaster University **Collaborator:** Merck
NCT01288014 (Observational) *On*-going http://ClinicalTrials.gov/show/NCT01288014	Cytokine Production and Immunity to Varicella Zoster Virus (VZV) in Elderly Recipients of Zoster Vaccine	N=26	Relatively healthy 60 to 80 years old	Immunogenicity	**Sponsor:** Columbia University **Collaborator:** Merck
NCT01262300 (Phase I) *On-going* http://ClinicalTrials.gov/show/NCT01288014	Vitamin D Supplementation And Varicella Zoster Virus Vaccine Responsiveness In Older Long-Term Care Residents	N=150	Adults aged ≥ 60 years and residing in a long-term care facility	Immunogenicity	**Sponsor:** University of Colorado, Denver **Collaborators:** - National Institute on Aging (NIA) - Mucosal and Vaccine Research Colorado - Merck
NCT01137669 (Phase I) On-going http://ClinicalTrials.gov/show/NCT01483378	Zostavax® in renal transplant patients:	N=40	Adults aged 18 years or older, with chronic kidney disease (CKD) who are scheduled to receive a living donor kidney transplant. Subjects will receive either ZOSTAVAX® or placebo no less than 4 weeks prior to their kidney transplant	Safety Immunogenicity	**Sponsor:** National Institute of Allergy and Infectious Diseases (NIAID)
NCT01331161 Completed	Systems Biology of zoster vaccine (Zostavax® in Young and Elderly (immunologic differences between	N= 77	33 healthy volunteers between the ages of 25-40 and 44 healthy volunteers between the ages of 60-79		**Sponsor:** Emory University

Protocol Number Study type	Study Title	Study population Intervention (N=) Comparator (N=)	Patient population	Focus	Sponsor / Collaborator
http://ClinicalTrials.gov/show/NCT01483378	a younger and an older group)				**Collaborator:** National Institute of Allergy and Infectious Diseases (NIAID)
NCT00921999 (observational) Completed http://ClinicalTrials.gov/show/NCT00921999	Immune Response to Varicella-Zoster Vaccination and Infection (To determine the immune system's response to the varicella virus, either in its existing form or given as part of a vaccine)	N=310	Healthy subjects 5 Years and older ·Individuals 18 years of age and older who have had or are receiving the varicella vaccine. ·Individuals 5 years of age and older who currently have chickenpox or shingles.	Immunogenicity	**Sponsor:** National Institute of Allergy and Infectious Diseases (NIAID)
NCT01474720 (Phase I) On-going http://ClinicalTrials.gov/show/NCT01474720	Zostavax in Systemic Lupus Erythematosus: Immunologic Response to Varicella Zoster Vaccination With Zostavax in Patients With Systemic Lupus Erythematosus	N=20	· 10 Healthy subjects aged 50 to 75 years · 10 Subjects aged 50 to 75 years with a Diagnosis of SLE according to ACR criteria for > 1 year; - Stable, mild disease activity as defined by a clinical SLEDAI score ≤ 4 - Current medical treatment for SLE stable for 4 weeks prior to screening - Acceptable immunosuppressive medications limited to Prednisone ≤ 10 mg daily, Methotrexate ≤ 20 mg weekly, Azathioprine ≤ 150 mg daily, Hydroxychloroquine ≤ 6.5 mg/kg daily	Safety Immunogenicity	**Sponsor:** Oklahoma Medical Research Foundation
NCT01506661 (Phase I) On-going http://ClinicalTrials.gov/show/NCT01506661	Zostavax in **Rheumatoid Arthritis:** Immune Response to Varicella Zoster Vaccination (ZOSTAVAX) in Subjects With Rheumatoid Arthritis	N= 20	· 10 Healthy subjects aged 50 years and older · 10 subjects aged 50 years and older with a diagnosis of rheumatoid arthritis according to ACR criteria for > 1 year - stable, mild disease activity as defined by a DAS28 score of 4.0 - Current medical treatment for RA has been stable for 4 weeks prior to screening -	Safety Immunogenicity	**Sponsor:** Oklahoma Medical Research Foundation

Protocol Number Study type	Study Title	Study population Intervention (N=) Comparator (N=)	Patient population	Focus	Sponsor / Collaborator
			Acceptable immunosuppressive medications limited to Prednisone ≤ 10 mg daily Methotrexate ≤ 20 mg weekly Hydroxychloroquine ≤ 6.5 mg/kg daily		
NCT00940940 (Phase IV) On-going http://ClinicalTrials.gov/show/NCT00940940	Safety and immunogenicity of Zostavax vaccine in patients undergoing living Donor Kidney Transplantation	N=40	Subjects aged 18 to 65 years, listed or will likely be listed for live donor kidney transplant within 1 month	Safety immunogenicity	**Sponsor:** University of Alberta
EudraCT Number: 2009-014268-20 (Phase IV) On-going *https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-014268-20/NL*	VZV vaccination to prevent herpes zoster after transplantation : To study if there is a role for prophylactic VZV vaccination prior to transplantation to boost the patients B- and T-cell repertoire and thereby reducing the incidence and morbidity associated with herpes zoster.	N=80	Subject and donor aged 50 years or older - Patients on waiting list for living-related kidney transplantation and their donors - Patients at least 1 month prior to kidney transplantation	Immunogenicity	**Sponsor:** Erasmus (Netherlands)

Source: *Adapted from Sanofi Pasteur MSD France. Marketing Authorization Holder submission file for shingles (herpes zoster) vaccine (live) Zostavax®. Submission date 12-04-2013.*

APPENDIX 5. INPUT OF DEDICATED REVIEWERS ON THE FIRST DRAFT OF THE ASSESSMENT

Seven reviewing organisations participated in the zostavax pilot: **RIZIV-INAMI-KCE (Belgium), HAS (France), BIQG/GÖG (Austria), MoH Cz Rep (Czech Republic), Regione Veneto (Italy), DGCF MSSSI (Spain) and DPA/MHEC (Malta).**

In the following table comments of the reviewers are marked in **orange**, whereas responses of the authors (A) are in **blue**.

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part I: Scope (see Chapter 1 of the pilot assessment)				
1. Was there a need to deviate from the Project Plan (protocol) in terms of clinical problem, population, intervention(s), comparison(s) and outcome(s)? If the answer is **NO**, please move directly to the Part II of the reviewer form.		**HAS:** Population of patients older than 50 years is concerned instead of patients older than 70 as planned previously by the company. (A): In the project plan it is already stated that it is about individuals of ≥ 50 years old.	**RIZIV-INAMI-KCE;** **HAS:** No deviation concerning clinical problem, intervention, comparison or outcome. The submitted dossier is in line with what was presented in the project plan. **BIQG/GÖG;** **MoH Cz Rep:** I think that the scoping part was rather well performed **Regione Veneto;** **DPA/MHEC:** Reported by authors pg 15	
2. Was a rationale included for the deviation of the scope that was proposed in the project plan?		**HAS:** It was recommended during scoping phase to keep the broader range of age. The population is in line with MAA wording.		**DPA/MHEC:** N/A
Part II: Methods (see Appendix 1 of the pilot assessment)				
1. If there was a need to deviate from the Project Plan (protocol) in terms of methods used, is it described in the Method's section of the pilot?	**HAS;** **Regione Veneto;** **DPA/MHEC.**	**RIZIV-INAMI-KCE:** Preliminary evidence table: Was antiviral therapy needed with acute Zoster? (A): Acute zoster can be treated (analgesics, antiviral drugs etc). But this assessment is not dealing		**BIQG/GÖG:** Not applicable, due no deviation from project plan in terms of methods.

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
		with treatment; it is about prevention of HZ **MoH Cz Rep:** There was practically no deviation required		
2. If there was no manufacturer's submission file available or the received submission file was incomplete, biased or outdated, did the authors conduct a more detailed search?	**BIQG/GÖG;** **DPA/MHEC.**	**HAS** A non-systematic review has been done because of the short timelines.	**RIZIV-INAMI-KCE** No systematic literature review (page 35) (A): It is mentioned in the report: not feasible in due time. To meet the comments of the reviewers, an update of the literature search carried out by the MAH SPMSD has been performed.	**MoH Cz Rep:** It was submitted the Value dossier by MAH, Authors of the assessment also performed some literature search. Hence we can say that the as much as possible evidence was tried to find/ described. **Regione Veneto:** It is not specified
3. Are inclusion/exclusion criteria for selection of the studies described in appropriate detail?	**HAS:** Both RCTs presented by the applicant were taken into account. **BIQG/GÖG;** **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**	**RIZIV-INAMI-KCE (Belgium)** not always (A): The in- and exclusion criteria of the ZEST (Schmader) has been added now. **MoH Cz Rep:** This issue could be discussed further in a more precise way. However, obviously all relevant evidence was captured.		**DPA/MHEC:** Not clear
4. Are the quality appraisal tools appropriate?	**RIZIV-INAMI-KCE;** **HAS;** **BIQG/GÖG;** **MoH Cz Rep;** **DGCF MSSSI;** **DPA/MHEC.**	**Regione Veneto:** A non-systematic review has its limits but we agree on the difficulties due to the timeframe		
5. Is the type/presentation of evidence (e.g. Meta analysis, qualitative synthesis, GRADE)	**HAS;** **BIQG/GÖG;** **MoH Cz Rep;**		**RIZIV-INAMI-KCE** No GRADE score in Appendix 1, though announced on page	

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
appropriate for this analysis?	**Regione Veneto;** **DGCF MSSSI** **DPA/MHEC:** considering time limits and data availability		35 (A): As mentioned on page 35, meta- analysis was not feasible due to lacking of information. To meet this point, a trend analysis was performed to estimate the age dependency of the outcome parameters (in case of sufficient data).	
6. Is the risk of bias sufficiently assessed, both on study level and on an outcome level?	**RIZIV-INAMI-KCE;** **HAS;** **BIQG/GÖG;** **MoH Cz Rep;** **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**			
7. Is the choice of study types appropriate to the population, intervention(s), comparison(s) and outcome(s)?	**RIZIV-INAMI-KCE;** **HAS:** RCTs are gold standard. Placebo as comparator is justified as no other preventive method is available. Population and outcomes of both studies are relevant. Products used in both RCTs are not the same but a bridging study has confirmed non-inferiority. **BIQG/GÖG;** **MoH Cz Rep:** Yes, all relevant evidence was captured **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**			
8. Are the types of studies to be included (randomised trials, quasi-randomised trials or	**RIZIV-INAMI-KCE;** **HAS** **BIQG/GÖG;**			

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
other designs) described?	**MoH Cz Rep;** **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**			
9. If it was relevant to include data from indirect comparisons, is this step justified and the methods of indirect comparisons sufficiently described?	**HAS** **BIQG/GÖG;** **DGCF MSSSI.**	**MoH Cz Rep:** Because of the type of the intervention and its use, there is currently "no other" available intervention.		**RIZIV-INAMI-KCE:** Not relevant **Regione Veneto:** It seems the authors did not find this need (A): Given the choice of comparator we agreed in the project plan (placebo), an indirect comparison is not an issue. There is no other drug available for the prevention of herpes zoster. **DPA/MHEC:** N/A As Non-systematic research used
10. Are appropriate methods of measuring each outcome and appropriate time points for measurement identified?	**HAS** **BIQG/GÖG;** **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**	**MoH Cz Rep:** It was performed the maximum possible, however still there is some uncertainty about long-term effectiveness. (A): Doubts about the long-term effectiveness (eg whether a booster will be needed) is mentioned in the report. This point will be stressed.	**RIZIV-INAMI-KCE** No consensus for burden of illness and PHN (A): There is indeed no European consensus. In the report we follow the definition of the pivotal studies and mentioned it in the text.	
11. Details on sources of information and literature search strategies provided? **RIZIV-INAMI-KCE:** But no systematic review; (A): A full systematic review in due time was not feasible. To address this point, an update of the literature search carried out by the MAH has been performed. Information about search strategies, databases etc is mentioned in the submission file. **DPA/MHEC:** Where not highlighted as not found or not clear.				

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
(A): Is being adjusted by referring to the literature search by SPMSD .				

Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
HAS; **BIQG/GÖG;** **MoH Cz Rep:** Not very much described **Regione Veneto;** **DPA/MHEC:** Not detailed	**RIZIV-INAMI-KCE;** **HAS;** **BIQG/GÖG;** **MoH Cz Rep;** **Regione Veneto;** **DPA/MHEC.**	**HAS:** Not stated. **BIQG/GÖG;** **MoH Cz Rep;** **Regione Veneto.**	**HAS:** Not stated. **BIQG/GÖG.**	**HAS:** References used for the assessment were provided. **BIQG/GÖG:** n.a. **Regione Veneto;** **DPA/MHEC.**	**HAS;** **BIQG/GÖG;** **Regione Veneto;** **DPA/MHEC.**

12. Information on basis for the assessment and interpretation of selected data and information?

Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?
HAS; **BIQG/GÖG;** **Regione Veneto:** It is generally described but I would suggest a more detailed explanation. In the "project approach and method" at page 35: the authors refer to EUnetHTA guidelines but it could be useful to mention what we intend for internal and external evaluation. (A): An explanation about the internal validity and applicability has been added in the line of the guidelines.	**RIZIV-INAMI-KCE;** **HAS;** **BIQG/GÖG** **MoH Cz Rep;** **Regione Veneto:** The applicability tables well summarize the applicability criteria. Additionally, It is reported in every RC if a quality assessment was made, but it is not very well explained how the authors made it.	**RIZIV-INAMI-KCE;** **HAS;** **BIQG/GÖG;** **Regione Veneto:** I couldn't find any reference to this point. (A): In most cases, the method of data synthesis is narrative. We thought that this is reasonable in respect to the limited timeframe of the assessment, so we did not make a further discussion. In the second draft, a trend analysis of the age-dependency of the outcomes has been added. A description of the trend analysis is added.

13. Do you agree on the selection of the assessment elements and the justification for not including specific elements?	**RIZIV-INAMI-KCE;** **HAS;** **BIQG/GÖG** **MoH Cz Rep;** **DGCF MSSSI;** **DPA/MHEC.**			**DPA/MHEC:** Is there a more updated one that document sent on 17th April? (A): the literature search as done by the MAH has been updated in June 2013. No relevant trials have been missing.
14. If there was a need to deviate from the Project Plan in terms selection of assessment	**BIQG/GÖG (Austria);** **Regione Veneto;**			**RIZIV-INAMI-KCE** Not applicable **HAS**

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
elements, is the change justified?				Not relevant. **MoH Cz Rep:** Not applicable. **DPA/MHEC:** Not found in document
Part III: Description of the evidence (see appendix 1 of the pilot assessment)				
1. Do you agree on the data extracted from the included studies? (See Table [X]. Characteristics of the randomized controlled studies and Table [X]. Relevant non-RCTs identified)	**RIZIV-INAMI-KCE;** **HAS;** **BIQG/GÖG;** **MoH Cz Rep;** **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**			
2. Do you agree on the risk of bias tables?	**RIZIV-INAMI-KCE;** **HAS;** **BIQG/GÖG;** **MoH Cz Rep;** **Regione Veneto:** Yes but I would explain the 2 question marks for the Pain – No other aspects according to risk bias. (A): The question mark is changed by 'unclear' with a note: The risk is unclear due to the high risk of other parameters. **DGCF MSSSI;** **DPA/MHEC.**			
3. Do you agree on the applicability tables?	**RIZIV-INAMI-KCE** We agree on all applicability tables! **HAS;** **MoH Cz Rep;** **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**			

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part IV: Results (See Domain Reports & Result Cards of the pilot assessment)				
Health problem and current use of the technology				
1. Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged populations, where it occurs, how it is diagnosed, symptoms and consequences)?	**RIZIV-INAMI-KCE;** **HAS;** **BIQG/GÖG;** **MoH Cz Rep;** **Regione Veneto:** Yes it is very complete; **DGCF MSSSI;** **DPA/MHEC.**			
2. Are the supporting references current and do they provide an international picture of the problem?	**RIZIV-INAMI-KCE;** **HAS:** Yes, data from 9 European countries are presented, dated 2000-2013. **BIQG/GÖG;** **MoH Cz Rep;** **Regione Veneto:** Yes, many Countries are treated in detail; **DGCF MSSSI**	**HAS:** Population of 50+given for all 27 EU countries. Not all people aged 50+ will be eligible for the vaccination so the estimate represents the hypothetical maximum of people that could benefit from the vaccination. (A): A question will be put to the MAH to clarify the estimation of persons with a contraindication for Zostavax. **DPA/MHEC:** A non-systematic research had to be used. Certain areas lack real life information but has been reported by authors. (A): question is answered by the reviewer self.		
Description and technical characteristics of the technology				
3. Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	**RIZIV-INAMI-KCE;** **HAS;** **BIQG/GÖG;** **Regione Veneto;**			

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
	DPA/MHEC.			
4. Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	**BIQG/GÖG;** **MoH Cz Rep;** **DGCF MSSSI**	**HAS** Not relevant as comparator is placebo. **Regione Veneto:** As there is insufficient evidence to determine whether the pain is influenced by Zostavax and the guidelines recommend the use of oral antiviral agents for the treatment of HZ, I would better critically explain results in pain management of preventing with comparison to cure HZ. (A): According to our report, pain reduction after Zostavax can not be shown. The composite outcome is too complex to be conclusive about any effect on pain once the patient develops HZ. Therefore a comparison with pain treatment will not be appropriate. Moreover, the therapeutic indication of Zostavax is prevention of HZ and PHN and not treatment.		**RIZIV-INAMI-KCE** Relevance? Comparator was placebo; **DPA/MHEC:** N/A
5. Are the supporting references current and do they provide an international picture of the problem?	**RIZIV-INAMI-KCE;** **HAS:** Yes, data from several EU countries are presented, dated 2003-2013. **BIQG/GÖG;** **MoH Cz Rep;** **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**			

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Safety and effectiveness				
6. Is the risk of bias clearly reported?	**HAS:** In risk of bias tables. **BIQG/GÖG;** **MoH Cz Rep;** **Regione Veneto;** **DPA/MHEC.**		**RIZIV-INAMI-KCE:** Reported but not discussed. (A): Only items denoted as high risk or unclear is explained in the tables (risk of bias tables 4-6). The reason of the doubt was mentioned. As requested: Additional text is being added.	
7. Is quality of data sufficiently evaluated?	**HAS:** Data coming mainly from 2 RCTs, SPC, EPAR. **BIQG/GÖG;** **MoH Cz Rep;** **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**		**RIZIV-INAMI-KCE** Not discussed e.g. potency of first batches in the study and of later batches (A): It was discussed in [B0001]: *What is the technology and the comparator(s)?*	
8. Are both relative and absolute effect measures presented for each dichotomous outcome?	**RIZIV-INAMI-KCE** **HAS:** Both relative and absolute risks are presented. **BIQG/GÖG;** **MoH Cz Rep;** **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**			
9. Are continuous data reported according to appropriate statistics (e.g. 'standardised mean difference' or 'weighted mean difference')?	**HAS;** **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**	**MoH Cz Rep:** This statistical data are rather presented in the appendices, however these appendices are not very much friendly for reader. The data is presented; there is no discussion about that. (A): The report is set up according to the model of the REA. We noted this comment	**RIZIV-INAMI-KCE** Only numbers and % (A): Data which are available were presented.	**BIQG/GÖG:** Not applicable, due no continuous data for safety/effectiveness section.

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
		and will keep the readability of the document in mind. In the first and second draft the focus will be gathering and validating of the content. In the last phase of the project, namely during editorial review, the report will be revised on grammar and visual aspects to improve the readability.		
10. In case of time-to event analysis, are hazard ratios (HR) and ratios of medians presented	**DGCF MSSSI;** **DPA/MHEC.**	**MoH Cz Rep:** This data were rather not applicable in terms of this intervention.	**RIZIV-INAMI-KCE** (A): Data not available.	**HAS:** Not relevant. **BIQG/GÖG:** Not applicable, due no time-to event analysis.
11. Are measures of the precision of the effect estimates presented or, in case of absence of this essential information, is this fact reported	**HAS:** Results are reported always with confidence intervals. **BIQG/GÖG;** **MoH Cz Rep:** Confidence intervals are presented. The relevance (clinical benefit) of each outcome is also discussed. **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**	**RIZIV-INAMI-KCE (Belgium)** Not always 95 % confidence intervals reported. (A): Unfortunately, it is not clear which data (and where) are missing. We will try to check on this.		
12. Is frequency of adverse events, frequency of occurrence, relative risk or number needed to harm (NNH) presented for the safety data	**HAS;** **BIQG/GÖG:** (NNTH) **MoH Cz Rep;** **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**		**RIZIV-INAMI-KCE:** (A): Frequency of side effects, RR and NNH are reported.	
13. In case where adverse events are	**Regione Veneto;**	**MoH Cz Rep:**		**RIZIV-INAMI-KCE**

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
incorporated in utility values of quality of life, is the source of quantification accessible?	**DGCF MSSSI**	This issue was not addressed. (A): adverse event is not incorporated as such in the QoL analysis.		Not applicable **HAS:** Not relevant. **DPA/MHEC:** Limited data available.
14. Do you agree that the results of this REA do not contain any errors or deficiencies?	**RIZIV-INAMI-KCE** well documented report in general; **HAS:** Yes, the assessment covers all predefined domains and an adequate methodology has been used for the assessment. **BIQG/GÖG;** **Regione Veneto;** **DGCF MSSSI**	**MoH Cz Rep:** I did not find any errors that could lead to any misinterpretation.		**DPA/MHEC:** Due to tight time lines and lack of expertise especially for statistical analysis this question cannot be answered clearly enough. (A): We interpret this as no comments from Malta for this moment.
15. Was the transformation of the surrogate outcomes into patient-relevant final outcomes considered?	**BIQG/GÖG;** **DGCF MSSSI;** **DPA/MHEC.**		**MoH Cz Rep:** Not so much. That is probably the biggest limitation. It was addressed BOI (by MaH) and considerably criticized/ assessed by authors. BOI is really hardly understandable, and it is questionable if this parameter has any impact on patients QoL. I think that further focus should be addressed to PHN and its impact on patients' QoL and their preferences. (A): The limitation of a composite endpoint like the BOI has been discussed in detail. Because of the	**RIZIV-INAMI-KCE** Not applicable; **HAS:** Not relevant.

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
			complexity of the endpoint we also present our doubts about the usefulness of this outcome. This does not mean we question about the impact of PHN on the patient's QoL. Conclusive data about it will be truly valuable. Unfortunately there were no such studies available.	
General				
16. Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed and synthesised data still answer the question?	**RIZIV-INAMI-KCE;** **HAS;** **BIQG/GÖG;** **MoH Cz Rep:** Rather yes, However still I have some problem with interpreting the data like lower incidence of HZ and possibly PHN. (A): A trend analysis has been added to capture a tendency in Zostavax efficacy in relation to population age. We hope this (and the figures with trendlines) will clarify the data. **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**			
17. Can the results be applied to the intended population?	**HAS;** **BIQG/GÖG;** **MoH Cz Rep:** Yes …with limitations mentioned above. **Regione Veneto;** **DGCF MSSSI;** **DPA/MHEC.**	**RIZIV-INAMI-KCE:** depending on the age categories		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
18. Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	**RIZIV-INAMI-KCE;** **HAS:** Judgements figure mainly in the discussions, which is appropriate. **BIQG/GÖG;** **MoH Cz Rep;** **Regione Veneto;** **DGCF MSSSI**			**DPA/MHEC:** Not always clearly distinguished difference between facts and judgement in text. (A): This is an important issue. It should be clear what the facts are and which conclusions can be drawn on that. If there are relevant limitations or assumptions, it should be stated. Unfortunately this statement is not further specified. We will pay extra attention to this point.
Part V: Summary of Relative Effectiveness				
1. Does the summary present a balanced representation of the content of the report?	**RIZIV-INAMI-KCE;** **HAS ;** **BIQG/GÖG;** **MoH Cz Rep;** **Regione Veneto;** **DGCF MSSSI**	**HAS:** Clinical effectiveness and safety are in the opposite order compared to the report. (A): the section about safety (page 7 in the first draft) is now placed before effectiveness. **DPA/MHEC:** Can a 'Limitations' section be considered? (A): the text in the summary is expanded to stress the uncertainties and limitations of the studies.		
2. Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?	**BIQG/GÖG;** **MoH Cz Rep:** Yes. However, still there are some doubts about added value of preventing HZ and PHN.	**RIZIV-INAMI-KCE:** partly, see question 7 on potency of batches in the studies **HAS:** 1) No conclusion can be		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
	These doubts will be always here, however more deeply should be described the impact on QoL and patients preferences due to infection of HZ and occurrence of PHN. (A): The impact of HZ/PHN on QoL in general is described in domain 1. Data on burden of disease associated with HZ and PHN is reported in A0005 and A0006. Limits and interpretation of QoL data are discussed also in the Applicability tables. A more deeply description in the section of effectiveness should be based on finding in the clinical studies. These data are not available. **Regione Veneto;** **DGCF MSSSI**	made about the long term efficacy of the vaccine as no data is available. This information might be added. (A): Uncertainty about the long term effectiveness is addressed in D0011E. 2) The level of protection against reactivation of VZV is also uncertain in patients who become immune-compromised later (immunodeficiency states, immunosuppressive therapy etc.). No recommendation for eventual revaccination can be given due to lack of data. This information might be added. (A): See former point. Uncertainty about the long term effectiveness is addressed in D0011E. This included every vaccinee including those who will get immune compromised by aging or by diseases. 3) The risk of HZ is significantly higher in immune-compromised patients so the prevention of HZ has particular importance in this population. The administration of the vaccine is contraindicated in the majority of immune-compromised states as sufficient evidence is missing. Nevertheless, this population		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
		would benefit the most from HZ prevention. This information might be added. (A): The effectiveness of zoster vaccination in immune compromised persons has not been shown because this group is excluded in the clinical trials. Although we agree this group has the highest need for protection, it cannot be stated they will benefit from Zostavax. This vaccine may even be not effective due to their reduced immune response. General: In the discussion of the summary is added some limitations of the studies. The abovementioned doubts have been integrated **DPA/MHEC:** Can a 'Limitations' section be considered? (A): Yes, the text is expanded to stress the uncertainties and limitations of the studies.		
Part VI: Other Considerations				
Have all relevant ethical, organisational, social and legal aspects been considered? (See Appendix 3 of the Pilot assessment)	**HAS;** **BIQG/GÖG;** **MoH Cz Rep:** Yes. Anyway, this issue should be rather addresses by each member state separately. **Regione Veneto;** **DGCF MSSSI**	**RIZIV-INAMI-KCE:** Shortly mentioned, see comments below. **DPA/MHEC:** More consideration should be given to organisational aspects B0008 (A): it is suggested to give more considerations. Unfortunately, this is not further specified.		

FURTHER GENERAL AND SPECIFIC COMMENTS FOR THE AUTHORS

Page	Line	Comments	Response of the authors
RIZIV-INAMI-KCE (Belgium)			
6	25	Add „whereas the formulation in the studies was mostly done with the frozen formulation“	Changed.
6	25	Add „Zostavax contains a live attenuated virus“ This is essential information in a summary on vaccine technology; hence readers can understand the exclusion of all immunodepressed patients from vaccination, unless supplementary evidence is given.	Changed.
6	25	Add „Zostavax is a booster vaccine, containing at high dose exactly the same strain as used in vaccines to prevent VZV-primo-infection“. Essential information on the nature of a booster vaccine is here required.	Changed.
7	44	Change „serious“ in „severe“	Changed.
7	45	Change „serious“ in „severe“	Changed.
8	10	Table is OK. Zostavax is indeed not reimbursed in Belgium.	Confirmation.
9	2	Column 6: change „serious“ in „severe“	Changed.
10	1	Column 6: change „serious“ in „severe“	Changed.
11	19	Change „serious“ in „severe“	Changed.
18	40	Change „reimbursed“ in „reimburse“	Changed.
22	2	Add essential information on the vaccine technology, namely „living attenuated virus“; also add „booster vaccine intended to be used in VZV-seropositive subjects” and “containing the same strain as in the vaccine against VZV-primo-infection but ZOSTAVAX contains higher content of virus”	Changed + Added in *B0001”* ZOSTAVAX is manufactured at a higher virus titre (14-fold higher potency) than varicella vaccine.”
23	33	No information is available on the different potencies of vaccines used in the clinical studies. This aspect has large implications on the long-term vaccine efficacy and the need of a booster, as was published. Reference: Bilcke J et al. Kosteneffectiviteit van vaccinatie tegen winkpokken bij kinderen en tegen zona bij ouderen in België. Health Technology Assesmment, KCE Brussels 2010, Report , n° 151A. and reference: Bilcke J, Ongunjimi B, Hulstaert F, Van Damme P, Hens N, Beutels Ph. Estimating the age-specific duration of herpes zoster vaccine protection: a matter of model choice? Vaccine 2012;30:2795-2800.	Potencies are mentioned at pag.22 line 6-8 and in B0001. Suggested additional paper has been now considered in the report. Bilcke J et al. Kosteneffectiviteit van vaccinatie tegen winkpokken bij kinderen en tegen zona bij ouderen in België. Health Technology Assesmment, KCE Brussels 2010, Report , n° 151A is mentioned as: KCE. Kosteneffectiviteit van vaccinatie tegen winkpokken bij kinderen en tegen zona bijouderen in België. Health Technology Assessment (HTA). Bruxelles, 2010. KCE Reports 151A. Available at: https://kce.fgov.be (English summary, also available in French) In *A0005, A0006, B0010*. While Bilcke J, Ongunjimi B, Hulstaert F, Van Damme P, Hens N, Beutels Ph. Estimating the age-specific duration of herpes zoster vaccine protection: a matter of model choice? Vaccine 2012;30:2795-2800 has been added in *B0001*.
25	13	Change „serious“ in „severe“ according to EUnetHTA Guideline on Safety (February 2013). Indeed, the Common Terminology Criteria for Adverse Events gives a scale of severity not of seriousness of adverse events. In fact, you quote the correct definition of seriousness of adverse events further on, at page 139 line 13.	Changed.

Page	Line	Comments	Response of the authors
29	21	Add subtitle 'Mortality' as you added subtitles for other Clinical Endpoints	Added.
29	40	PHN is not a potential cause of death; the CTCAE-criteria you quote give for 'neuralgia' only severity grades 1-2-3, and thus no grades 4-5 (latter one is death).	Changed. PHN is placed between brackets now. Zoster can cause death, and PHN is a condition following zoster. So there is an indirect relationship.
32	26	A general remark on the Discussion of Clinical Efficacy. You could organise the endpoints in on-label and off-label endpoints, as we believe this is the very reason why people will read the EUnetHTA report beside the EPAR of ZOSTAVAX. The on-label endpoints are 1° less zoster events and 2° less PHN. The off-label endpoints are mortality rate, hospitalisation rate, quality of life, burden of illness and zoster pain solely. We congratulate the authors on the completeness of this chapter in the different Result Cards pp 155-195.	We'll try to reorganise the text in order to get a better presentation. The terms on-label endpoints and off-label endpoints will not be used because this will probably be associated with off-label indication and causes confusion.
32	39	'the condition of PHN can only exist in subjects who developed herpes zoster'. You could add for clarity 'either in the unboosted arm (placebo), either as breakthrough zoster cases in the boosted arm (Zostavax)'.	An additional sentence is added.
59	1	Off label risks. Add "immunodepressed subjects'. This will make the remark on page 91 line 3 of exclusion of immunodepressed subjects more consistent with this Result Card. Thanks for the impressive list of ongoing studies of Zostavax in immunodepressed patients.	Changed.
76	7	Change "is" in "are"	Changed.
82	11	I don't find the two Bilcke papers in the reference list at the end of Result Card A6.	Added.
107	31	Table is OK. Zostavax is indeed not reimbursed in Belgium.	confirmation
112	14	Add essential information on the vaccine technology, namely „living attenuated virus" and „booster vaccine intended to be used in VZV-seropositive subjects" and "containing the same strain as in the vaccine against VZV-primo-infection but ZOSTAVAX contains higher content of virus"	Changed.
196	3	Organisational domain. You could add the absence of a need for testing for VZV-seropositivity, before the administration of this booster vaccine.	Issue mentioned now in B*0008*.
197	1	Legal domain. You could add a remark on the possible legal consequences in case of zoster outbreak after vaccination. Either it is an outbreak of the endogenous VZV, either it is the Oka/Merck strain of the vaccine that is shedded. Both situations can be accurately tested with PCR but need not to be done in practice.	The risk of outbreak after vaccination is a general problem and not specific to zoster.
HAS (France)			
2		HAS is missing in the list of dedicated reviewers	Changed.
27	8	Wording "…increase is even more **significant** in the Zostavax…"	This is not about a change in P-value, but about the percentage individuals with ≥1 SAE. Therefore the sentence will be changed to: This increase is **significant and** even more in the Zostavax group.
96	10	Modify for better comprehensibility „…sample of Medicare**. These individuals** received or did not….."	Changed.
113	24 &	A very short explanation may be provided to justify the reason for having	The comparator of zostavax is placebo because no other drug has been

Page	Line	Comments	Response of the authors
	32	placebo as the appropriate comparator.	approved to vaccinate against herpes zoster. We motivated in this way our decision in *B0001.*
118	25	Wording "…Zostavax will most likely **be** administrated…"	Changed.
119	29	Modify for better comprehensibility „…sample of Medicare**. These individuals** received or did not….."	Changed.
Note: Typos and grammar mistakes were not corrected in accordance with the instructions given by the CVZ.			
Reimbursement status in France: No recommendation concerning Zostavax has been given. The product is not reimbursed in France for the moment and the company has not applied for yet.			
Overlap of result cards: In cases when several result cards of the same domain may be grouped together, it is preferable to do so, if this does not affect the comprehension of the report. Keeping all result cards separate respects the general idea but in cases when the cards have different heading but identical content its benefit is low. The approach adopted by CVZ is therefore encouraged.			
BIQG/GÖG (Austria)			
8	10	Reimbursement status for Austria is correct. (note: authorization in 2006, but currently not on market in Austria)	Specified at pag.107 that Zostavax is currently not on market.
107	34	Reimbursement status for Austria is correct.	Specified at pag.107 that Zostavax is currently not on market.
MoH Cz Rep (Czech Republic)			
7	5	In the Czech Republic the vaccine is neither reimbursed nor presented on the market, i,e. not used by physician and required by patients, by now.	Changed at page. 110.
154,159		Regarding the presentation of the results on the result cards, in my perspective, it is easier to read it like it is now. Since to address particular question will lead to overlapping (as it is mentioned). Generally, the effectiveness data are usually very much connected to each other. It makes rather sense to clearly address all issues within one text instead of direct/ literal answering of particular question.	Czech Republic agrees to the chosen setup of the results cards.
		It can be considered by reader that some parts of the appendices are too long and it is hard to find the key information there.	Unfortunately it is not specified where improvements can be made.
Regione Veneto (Italy)			
6 and 92	8 29	I don't very much understand "188.17 million people". Besides I think it is most common in Europe the use of coma instead of point, I would find more immediate to report the precise number 188.170.000. Additionally, if HZ can only occur in people who have had varicella, has all the population > 50 (excluded the categories reported in A0007) to be vaccinated?	Changed.
7	17	The table is at page 44 not 43	It is indeed page 44. PM for the final version in case the page numbering is changing again.
68	46	I don't understand why the information is not completely transferable	Changed.
95	10	The SPMSD estimation of 5-10% of population that can be excluded from the target can be confirmed by experts? It seems very low	The MAH will be asked to explain and support the estimated percentage. Question to MAH: The MAH assumed that 5-10% of the total population will be contraindicated for a vaccination, e.g. due to a deprived immune status (caused by disease or treatment). Can SPMSD explain what the evidence (including the data sources) is for this range estimation and whether this range can be

Page	Line	Comments	Response of the authors
			extrapolated to other member states of EUnetHTA? In case that age is influencing this percentage, it should also be clarified per age group, too.
105	13	I would say the information is critical	Information in A0025 (How is the health condition currently managed according to published guidelines and in practice?) deal with HZ treatment, while Zostavax is a vaccine aiming to prevent HZ. For that reason, the information contained in A0025 is considered as important and not critical. It's relevant for HZ, but not critical in terms of its prevention.
107	7	why the information is not completely transferable?	Marketing authorisation status could have a national/local dimension. For instance, we didn't report regional decision in A0020. Therefore, it was considered only partially transferable. Furthermore, the marketing authorization worldwide can change.
102	24	As explained in part IV – I would critically explain the differences between preventing and curing HZ (with reference to the guidelines that recommend the use of oral antiviral agents for the treatment of HZ) in the management of pain. I would better critically explain results of preventing with comparison to cure HZ. (page 102)	Zostavax is a vaccine whose aim is to prevent HZ. While mentioned antiviral agents aim to treat HZ when it's already visible. No guideline is available on prevention of HZ or prevention of HZ related pain when the disease isn't yet diagnosed. Current guidelines deal with prevention of HZ related pain when HZ is already under way. The basic distinction between prevention and cure was at the base of the decision to adopt placebo as the only comparator of Zostavax.
119	4	I would consider the information as important but not critical	Changed.
119	11	I would consider the information partly transferable as the administration of a vaccine is different from Country to Country	Changed.
122		Why B0009 is not complete? Even if there is no special needs of supplies, the card can be completed in Importance and transferability	Changed as Important and Completely transferable.
124	39	I would consider the information as important but not critical	Changed.
		The medicine obtained EMA marketing authorisation in 2006. According to the WP5 Work Plan the pilot starts before EMA authorisation, therefore we wonder why an authorised medicine was selected and whether this pilot will be useful to test the process. Moreover, in Italy the medicine was evaluated in 2010 and it was decided, according to the company's request, to not reimburse it.	Regarding the topic identification criteria, based on discussions with WP5 members during face to face meeting in Diemen (NL) and comments received from WP5 members, it was decided that we will strive to select also some pharmaceuticals that are on the market for a longer time. We would like to gain diverse experience with the methods developed in Strand A. This idea has been also included in the WP5 3-year plan.
DPA/MHEC (Malta)			
107	34	In Malta Zostavax is available but not reimbursed	Changed at page. 110.
155	2	It is a good idea to combine research questions. Probably this should be adapted per pilot. Same problem was observed in the Pazopanib pilot and though questions may be similar, answer may still vary depending from which point of view it is taken.	Malta agreed to the chosen approach.
160	15	Please refer to previous comment.	Malta agreed to the chosen approach.
		General comment: As in this instance it was reported that non-systematic research had to be done due to time limitations, could this be further investigated on how to avoid e.g. involving more agencies or more authors within same agency.	Suggestion for improvements are welcome. Involving more agencies or more authors would not per se speed up the process linearly. Enlarging the team will urge for more communication, which can also be time consuming. It is about finding as well as judging the information in conjuction to the research questions and ultimately bring relevant information as a whole. The biggest limitation is the (intended) timeline of 90 days, which is too short to perform a

Page	Line	Comments	Response of the authors
			thorough systemic literature review, too. In this case, we solve this partly by updating the search of the MAH, performing a non-systematic review where we feel needed, and through feedbackprocedures of the reviewers. In our opinion, the chance of missing relevant information is limited to a minimum. This method is only possible in case a submission file is available. In case this is lacking, this issue has to be tackled by another way. Team expansion or extention of the timeline are possible solutions.
		General comment: Due to time constraints is it possible to list all limitations, missing data, unanswered questions in a section in order to be considered as evidence gaps/ future HTAs at a more national level?	In the second draft we add text about relevant limitations of the studies.

APPENDIX 6. INPUT OF MAH (SPMSD) AND WP5 MEMBERS ON THE SECOND DRAFT OF THE ASSESSMENT

MAH's Comments:

Page	Line	Comments	Comments from the authors
general		MAH is ***Sanofi Pasteur MSD*** (not sanofi) – please correct throughout the report	OK. We will refer the MAH as Sanofi Pasteur MSD or SPMSD for abbreviation.
general		The manufacturer/producer of Zostavax is ***Merck Sharp & Dohme*** – please correct throughout the report	Changed.
general		Typos & grammar mistakes were not corrected in accordance with instructions from CVZ, as editorial review is planned at a later stage of the process.	Yes, grammar and typos will be checked and corrected during the editorial review.
general		Comments on the 2nd draft of Zostavax rapid REA pilot: - The draft needs to be reviewed globally and harmonised before publication, as currently many redundancies and inconsistencies remain, partly linked to issue in ordering the information within subsections and probably due to various writers & reviewers. - - Set up appropriate process so that confidentiality is ensured on the whole set of data disclosed in confidence by the MAH (eg. some data from PSUR – highlighted confidential- remains in current draft). Comments on data sources: - Data sources should refer primarily to the EU SPC/EPAR (as per EUnetHTA guidelines) for clinical effectiveness & safety – other publically available data are nevertheless major in complementing EU SPC/EPAR.	 - Naturally, redundant repeats and inconsistencies should be avoided. In the final phase the text will subjected to an editorial review. - - according to us the procedures are sufficient to ensure confidentiality. No data are published that should be considered as confidential. As communicated before (see also the document summary of the scoping meeting): it should be possible to cite from the submission file for the purpose of drawing up the report. - For this assessment, we consider every source of information available, as long as this meets the criteria.[1]

[1] As stated in the summary of the scoping meeting on 26-02-2013 (CVZ-document 2013024091): Only data which can be verified (such as public data) can be used in the file. Unpublished research reports can only be involved in an initial assessment if the applicant provides the complete research data in a form that can easily be analysed and if it is possible to cite from them for the purpose of drawing up the report.

Page	Line	Comments	Comments from the authors
		- In accordance with HTA Core model WP5, rapid REA should recognise the published data coming from real-life and post-marketing experience & clinical plans (e.g. RMP, FUM) in countries out of EU, which is a key feature of Zostavax current pilot. - The national submission (NL) should ***not*** be used as a source of information for the rapid REA, especially as the scopes differ. In the current pilot draft report, it seems that both MAH submission file and Dutch files have been used and inappropriately mixed, when the rapid REA should have been based on the EU MAH submission file only.	- Data of the real life studies are now presented in D0017. - We are not aware that information that was not allowed has been used. Upon our request the MAH added the information that is about thee mortality figures in the Netherlands. According to us these figures are public data available at the website of www.cbs.nl. It is not correct to state that the assessment should only be based on the submission file. We are also considering other publications.
6	4 (table)	Population: As data sources are 2 different RCT, suggest ***removing 'subgroup'*** word + add age ranges ***70-79*** (as mentioned in table page 10).	The subgroup of 70-79 years will be added.
6	7	First sentence, suggest adding that: HZ is due to the reactivation of the latent VZV therefore almost all adults are at-risk.(see MAH submission page 10).	Information about reactivation is already mentioned in the next sentence. We do not feel the text has to be changed.
6	12	Bacterial infections are complication of HZ – not risk factors (refer to comment in A0003).	We eliminated bacterial infections among risk factors here and in A0003 (pag.67 table, pag. 68 line 36).
6	13	Suggest rewording to clarify both rash and pain symptoms: 'Although the rash is the most distinctive feature of HZ, the most frequently debilitating symptom is neuropathic pain which may occur during 3 time periods' […prodromal/subacute, acute, chronic] (source: Johnson et al, 2007 – reference 19 of the MAH submission file).	It has been reworded as: "Herpes zoster is clinically characterised by rash and pain. The most frequently debilitating symptom is neuropathic pain which may occur during three phases of HZ: subacute herpetic neuralgia, acute herpetic neuralgia, chronic and post-herpetic neuralgia (PHN)."
6	18-19	There is no agreed definition of PHN in the scientific community esp. regarding to the time at which HZ-associated pain become PHN and whether pain intensity should be included. However, recent data and concepts trend to define PHN as significant pain persisting for 3-4months after rash onset, with pain score ≥3 on a	Text has been reworded.

Page	Line	Comments	Comments from the authors
		VAS. (refer to MAH submission file ref 19 – Johnson et al 2007). This is also the reason why in the pivotal SPS (Oxman, 2005), clinical endpoint on PHN was "pain persisting or occurring at 90 days after the rash onset with pain score ≥3". ⇨ Please reword text accordingly to include ***3-4 months PHN definition.*** This is consistent with result card A0002 page 65 lines 1-2-3 and country-specific figures (A0006)	
6	19	***Burden to the patient*** is partially described: suggest adding key elements on HZ & PHN ***impact on HRQoL and ADL*** (refer to A0005 - page 74: lines 22 and following).	Text has been added (p.7, line 4).
7	6-7	European guidelines dealing with prevention of HZ do exist in Europe: Official ***recommendation*** do exist in UK (70-79), Austria (50+), Saxony in Germany (50+), Greece (60+) – see page 9 of the pilot – please modify text accordingly.	Lack of common European guidelines, and not lack of national guidelines published in separate European countries was meant in the text. This issue has been clarified.
7	18	- Specify '***antivirals***' – drug is imprecise. - Antivirals were previously indicated for the treatment of PHN but lost recently this indication.	Added oral antiviral agent. We agree that antivirals aren't indicated for PHN. In A0025 in table at pag. 100 and at pag.101 (line 2) antivirals are not mentioned (Current treatments for postherpetic neuralgia are tricyclic antidepressant drugs (TCAs), alpha-2-delta-ligands, opioids and topical agents.). However, as reported at pag. 101 (line 1) "Aciclovir, valaciclovir, famciclovir [Schmader 1999; Sacks 2013] and brivudin are also utilized in the treatments of PHN." Therefore, sentence at pag. 7 (line 18) has been reworded in order to avoid confusion: "The oral antiviral agent can reduce the duration and severity of pain, but it cannot prevent the onset of PHN".
7	27	Use of 'booster vaccine' is confusing in vaccinology as it refers to administration of additional doses at distance of a primary dose. As you want to explain the mechanism of action, we suggest changing to: ***'Zostavax boosts VZV-specific cell-mediated immunity'*** (see EU SPC – 5.1. mechanism of action).	Sentence has been revised.

Page	Line	Comments	Comments from the authors
8	8	- Please mention that **25 RCTs have been conducted** (immunogenicity, safety & efficacy), in order to provide an accurate view to EUnetHTA members. - Safety has been studied in more than 2 RCTs – please refer to MAH submission file – page 73. - OK with 2 pivotal RCTs for efficacy (SPS and ZEST). - Add ***short & long-term persistence studies*** in the available evidence. - Add ***evidence on effectiveness*** from Tseng et al jama 2011, Zhang et al jama 2012, Langan PLoS medicine 2013 (refer to pages 101-102 + complementary of MAH submission file). Please refer to comment on appendix 1 – selection of evidence.	Text has been adjusted. Furthermore, an appendix (appendix 5 of the submission file about the clinical development Zostavax; p 113-126) has been added. Real life data are incorporated in D0017.
8	13	Correct median follow-up is ***3.12 years*** (and not 3.4) – see page 28 line 19.	This has been corrected.
8	13	Please add the following, which helps for the interpretation of VE: ***It should be reminded that in both RCTs it was specified in the protocols that the physician have to offer to subjects with HZ, an antiviral drug and standard-of-care treatment for pain, according to the judgement of the physician, in accordance with usual clinical practice.*** (Oxman 2005 & Schmader 2012)	In our opinion, this kind of background information does not fit into the summary.
8	17	The BOI was the primary clinical outcome only for the SPS – not for the ZEST where incidence HZ was the primary criteria.	The original primary outcome of the ZEST was indeed vaccine efficacy (protocol on www.clinicaltrials.gov) and reflected in the publication of Schmader as incidence of HZ. The words “clinical studies” is therefore changed to ‘SPS’.
8	17	Note that BOI in ZEST was defined at 21 days (and not 90 days as SPS).	It is already noted that the BOI in het ZEST has another definition than the SPS. This difference was mentioned in the report (e.g. on page 10 in note under the table).
8	23	Change to: ***Twelve*** ongoing RCTs (i.e. CSR not yet available), change also in table page 48: add studies NCT01391546 – intramuscular versus subcutaneous administration route: immunogenicity & safety of ZOSTAVAX http://clinicaltrials.gov/ct2/show/NCT01391546?term=NCT+01391546&rank=1 & NCT00851786 - HIV-Infected Adults on Antiretroviral Therapy: immunogenicity & safety of ZOSTAVAX	Both NCT01391546 and NCT00851786 have been added to Table of ongoing studies. NCT00851786 was already considered (Center for Biostatistics in AIDS Research. Live Zoster Vaccine in HIV-Infected Adults on Antiretroviral Therapy. Clinical trial

Page	Line	Comments	Comments from the authors
		http://clinicaltrials.gov/ct2/show/NCT00851786?term=HIV+%26+zostavax&rank=1	NCT00851786. Viewed on 06/05/2013 http://clinicaltrials.gov/ct2/show/results/NCT00851786) and discussed in C0001A (Safety domain).
8	39	Suggest precise "The vaccine efficacy in ***preventing HZ*** (51% in average ***among the ≥60***) is age-dependant, etc.	The specific (age dependent) data is mentioned in the sentence thereafter. Because data about 50-59 is indeed not included in the mean of 51%, the text is changed to: on average over 50%).
8	40	In accordance to the HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals ("The relative benefits of the new pharmaceutical are discussed in the clinical effectiveness domain and can be determined under experimental conditions (e.g. within the protocol of a randomised controlled trial [RCT]) or under routine conditions"), we suggest to add ***real-life effectiveness on incidence of HZ***: - Among ≥ 60: ***55%*** (HR: 0.45 – CI 0.42-0.48) – in all age strata eg HR: 0.44 (CI: 0.35-0.56) for ≥ 80 & ***VE on HZO: 63%*** (HR: 0.37 – CI: 0.23-0.61) (Tseng et al. Jama 2011) - Among ≥ 65 immunocompetent: ***51%*** (CI 41-59%) (Langan et al. PLoS Medicine 2013) See MAH submission file pages 102-103 + complement	Data of the real life studies are now presented in D0017.
8	42-45	The way the effectiveness on PHN is expressed "PHN is lower after vaccination, but this effect seems to be related to the decreased incidence of HZ" should be further detailed and explained. - We suggest to copy/paste from page 29 line 40: ***"Overall, the VE PHN was 66.5% (95% CI: 47.5 to 79.2; P<0.001) as compared to the total population. There were no significant differences in the VE PHN when the results were stratified according to age".*** - Moreover, to explain this stable vaccine efficacy on PHN whatever the age , taking into consideration the vaccine effect in preventing PHN beyond its effect on the incidence of HZ, in relation to the age , as follows: ***"Efficacy for the prevention of HZ was highest among 60-69 and declined with increasing age. However, no significant differences among persons aged 60-69 versus these aged ≥70 years in vaccine efficacy at reducing PHN, probably because the independent effect of reducing PHN among patients who develop HZ was greatest among persons 70-79."***– see MAH submission file	The text in the summary about VE PHN is rewritten.

Page	Line	Comments	Comments from the authors
		pages 92-93 & CDC MMWR, 2008 & Oxman, Hum Vacc 2007 p66. See also comment for page 29 line 42 It should be noted that vaccine efficacy on PHN in the age group of 50-59 years old was not investigated as due to the epidemiological features of PHN which occur more frequently after the age of 60 or even 70.	This is already mentioned in the text as: 'due to low incidence'.
8	45	Please mention as well that: "The frequency, duration, and quantity of use of various medications to treat pain resulting from HZ were similar in both groups. Thus, differences in the use of pain medication did not inflate the estimates of VE BOI or VE PHN. This suggests that the overall effect of the vaccine was ***in addition to*** any benefit that may have been obtained from timely medical therapy. " (Oxman 2005, Schmader, 2012 & Zostavax SmPC New Zealand http://www.ncirs.edu.au/immunisation/fact-sheets/herpes-zoster-vaccine-fact-sheet.pdf)	Background information does not belong to the summary. Moreover, there is insufficient data to support the conclusion of the MAH that the pain treatments are similar in both study arms. Specific data about the pain treatments are lacking.
8	46	Mention real-life effectiveness: ***VE on hospitalisation: 65%*** (HR: 0.35 – CI: 0.24-0.51) among ≥ 60y – source Tseng et al. jama 2011 – see MAH submission file page 102.	Data of the real life studies are now presented in D0017.
9	1	As presented in the MAH submission file pages 83 & 84 (reference to EU SPC), evidence on the e***ffect of ZOSTAVAX on pain*** is the following: - Prevention of ***HZ cases with severe pain*** (score>600) in the overall population aged ≥60 years: ***73%*** (46-87%) - ***Among vaccinated subjects who develop HZ: significant reduction of the overall acute & chronic HZ-associated pain over 6 months:*** 22% reduction (p=0.0008) in the severity-by-duration score & 52% in the risk of having HZ with severe & long lasting pain (score >600). - ***Among vaccinated subjects who develop PHN: 57% reduction in the severity-by-duration score*** in the period from 90 days (after rash onset) to end of the follow-up (p=0.016). Sanofi Pasteur-MSD requests a revision of the judgement 'insufficient' regarding the evidence on pain (see comment on D0005).	One of the key elements of this assessment is to critically review the methodological limitations of the different endpoints presented like for instance information on pain. We have clearly described in the different parts in the text that there are serious limitations on how pain has been assessed in the different RCTs. We did not receive any additional information that has clarified these limitations, so there are no reasons to make changes in these statements in the assessment report.
9	8 table	Target population recommended and funded in the UK is ***70-79*** (instead of 70+) – see page 22	This has been changed in the text.

Page	Line	Comments	Comments from the authors
10	Table	- Suggest to use primarily EU SPC as sources of information for Health benefits & harms table – source F, M, Sm, Sk, O should complement EU SPC/EPAR.	As mentioned before, we are not limited to a single data source. In the SPC of Zostavax, not all data about the subgroups as mentioned here can be found. So referring to the SPC will be incorrect/incomplete.
		- Column 4:VE incidence HZ – source is O rather than F. Column 6: change title to: VE ***proportion of PHN among*** subjects who develop HZ post-vaccination (and not compared to) ; ***add value in cell ≥70y: 47% (13-67%) source M or CAN as it is available in the latest Canadian SmPC (page 19) available at:*** http://www.merck.ca/assets/en/pdf/products/ZOSTAVAX-PM_E.pdf	Title of this column is changed. Data about ≥70 years has been added.
		- Column 8: VE BOI – results overall are: ***61.1% (and not 1.1%)***	It has been corrected.
		- Suggest harmonisation of number of decimals	Corrected here. Harmonisation the number of decimal is taken into consideration as much as possible. It is noted that rounding the numbers has the disadvantage of less recognition of the figures (not exactly the same numbers).
		- VE for 50-59: Note that VE HZ you present in the table is not that of the EU SPC: you mention M-ITT (72%), while EU SPC is referring to ITT (70%) Note: BOI in ZEST refers to 21 days (and not 90 days as in the SPS).	We choose to report the mITT data of the ZEST because data of the SPS is also mITT. The difference in the BOI definition is marked in the note below the table.
		- Quality of body of evidence of VE BOI is rated as "low", when this level is not justified nor consistent with result cards D0002B2, D0005, D0006, D0011A&C in pages 159-163. We have provided in pages 83-84 of the MAH submission file the HZ severity-of-illness scores e.g. components of the composite endpoint: BOI. BOI was co-primary endpoint of the pivotal SPS with incidence of PHN, endpoints considered as valid by both EMA and FDA. Moreover, a specific method for assessing the combined effect on disease incidence, severity by duration weighted for age group was used (Oxman 2005 & Chang 1994). To address your concern we enclose a methodological note (Annex 2). Referring to your guidelines on "HTA Core Model for rapid REA", this note states that: • BOI is not the single primary endpoints of SPS	The critical review of the composite endpoint of BOI has been discussed in the mentioned results cards. Based on these findings we came to this conclusion. For motivation of the choice, the methodological limitation of this outcome we refer to the report.

Page	Line	Comments	Comments from the authors
		• Number of components are limited to 2 (HZ incidence and severity-of-illness scores/AUC) • Justification that BOI is a suitable endpoint has been justified in Coplan, 2004 ; Chang, 1994; Oxman 2005 This may represent a background to rate the Quality of body of evidence of VE BOI as "non-considered according to Core-Model", rather than "Low" that could be criticised in the absence of justification. - Order of the rows according to RCT sources: Start with 50-59 (ZEST) and then present all others including overall (≥60), 60-69, 70-79, ≥80, ≥70.	The table is rescheduled to improve readability. The ordering of the age groups is also adjusted.
ab11	3	Why studies of real-life effectiveness are not taken into account, as complement and confirming clinical efficacy evidence? (Tseng, Jama 2011 – ref 236 of MAH submission file, Langan PLOS med 2013 – complementary submission)	Data of the real life studies are now presented in D0017. Langan is also mentioned in B0005 and A0011.
11	general	- Discussion should cover all 4 domains of the REA: health problem is missing in current version. - Discussion is currently focusing on the limitations of the results and should probably be more balanced, notably with the availability of 10 years efficacy, safety and real-life effectiveness data (very rare when a new drug/ vaccine is assessed)	The discussion section refers to discussion of studies and their results. Crucial points are reported. In the discussion section current version on the model for rapid REA has been followed. For details, please see the Model (p.61).
11	7	Suggest explaining the reason why PHN was not a criteria for the ZEST (in 50-59): "The incidence of PHN is not studied in the ZEST study for subjects 50-59 yrs-old, ***due to the epidemiological features of PHN which occur more frequently after the age of 60 or even 70.***"	It was already mentioned in the text that it may even need a bigger population. The text has been expanded as follows: 'Further, because of its particularly low incidence in participants aged 50-59 years old, in ZEST, the incidence of PHN was not studied in this age group'.
11	7-8	*'e.g. cohort of HZ patients only'*: this seems not relevant - what would be the demonstration to follow ill patients as ZOSTAVAX is prevention? Effectiveness studies in ≥ 50y would allow answering the question.	This is a suggestion. The claim of SPMSD also includes the prevention of PHN for Zostavax. If this is an independent and solely acting effect of Zostavax, it could be demonstrated more conclusively. Research of Zostavax in HZ patient can clarify its effect on PHN beyond the effect on HZ.

Page	Line	Comments	Comments from the authors
			The possibility of a bigger population (including 50+) has also been mentioned, although the interdependence of the incidence of HZ and PHN will still be present.
11	10-14	Note that 'bridging studies' are current practice for several vaccines recognised by the EMA. Classically, clinical bridging studies generate immunogenicity data to support the extrapolation of data on safety and protective efficacy obtained under specific circumstances of use to other situations (e.g. changes in the production process, additional schedules and/or populations). Other vaccines exist in both frozen and refrigerated formulations (eg MMRV) and have followed similar clinical development with bridging studies. Please refer to EMA guidelines on clinical evaluation of new vaccines - page 17 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003870.pdf	In designing bridging studies, it is important to consider the critical immunological parameters for determining comparability of immune responses. EMA guidelines on Clinical Evaluation of New Vaccines requested comparative immunogenicity studies in case of formulation changes. In the study of Gilderman et al, the VZV antibody geometric mean titer (day 28), the VZV antibody geometric mean rise (day 1 versus day 28) have been chosen as primary endpoints. In this study, it was indicated by the authors that endpoints correlated best with protection to HZ. M.J. Levin and others [Levin 2009] criticized this assumption and indicated that there is no direct evidence that these endpoints are the 'best correlation' for immunity postvaccination. In elderly patients with HZ, the severity of the HZ correlates with the magnitude and tempo of VZV-specific T-cells (early effector and effector memory populations) appearance, but not with the magnitude of VZV-specific antibody. Levin also indicated that the paper of Gilderman provided no data on the relationship of GMR to HZ. In the sight of these discussions, we think that it is essential to mention these doubts on whether the Gilderman study has actually proven that both formulations of Zostavax have a similar vaccine efficacy.

Page	Line	Comments	Comments from the authors
			The reference to the EMA guideline has been added to the text.
11	15-17	Some evidence exist for specific groups (as mentioned in card D0011B): patients on chronic/maintenance corticosteroids (<20mg/day) & patients HIV+ treated by ART, and real-life effectiveness studies including immunocompromised conditions (AID) – Zhang Jama 2012 & Langan, 2013 Note that 90% of the HZ cases are in immunocompetent.	The text is nuanced to: there is limited information.
11	18-20	Remove ***vaccination*** => immunosuppressive medication exist however immunosuppressive vaccination not. You can refer to Langan, 2013 where such patients were included	Word has been removed.
11	21-25	BOI is primary endpoint only in the SPS (not in ZEST) – stud***y*** instead of stud***ies***	The word 'studies' is changed to SPS.
11	26-29	***Pain assessment and impact on ADL has been measured by the ZBPI***, questionnaire specifically adapted & validated in the ≥60, and specifying pain score thresholds for clinically relevant HZ/PHN pain. ZBPI has been proven to be sensitive to neuropathic pain. Refer to Coplan J Pain 2004 & Schmader 2010 (reference 112 & 215 of MAH submission file) Please revise the text accordingly (see comments for page 9 line 1 - page 59 - Appendix 1) + refer to A0005 page 73, lines 36-57.	Our comments on the pain assessment are discussed in the results cards. The mentioned publications have already been considered. No new information has been added.
11	38	Suggest rewording to be more precise and specific (reflecting REA results for clinical effectiveness domain): '…is more effective in preventing herpes zoster ***and post-herpetic neuralgia*** as well as HZ pain severity & burden than placebo.' The ***HZ*** incidence lowering effect is age-dependant…' Suggest adding: ***However, no significant differences among persons aged 60-69 versus these aged ≥70 years in vaccine efficacy at reducing PHN, probably because the independent effect of reducing PHN among patients who develop HZ was greatest among persons 70-79.*** *Or* ***However, older patients (aged ≥70 years) still benefited significantly from lower PHN incidence (67% reduction) and BOI scores (55% reduction).***	We think that the conclusions of SPMSD are not always substantiated by the presented data; therefore the suggestion will not be taken over. The assessment report presents results and the interpretation of these results. We do not think that statements that are not sufficiently substantiated by data should be part of a conclusion. The model for rapid REA, that is publically available on EUnetHTA website, clearly states on how the conclusions should be presented in the rapid REA. For details please see Model for rapid REA (p. 61)
11	42-43	Reconsider your statement in light if the above-comments (eg. evidence of	No additional new information has been

Page	Line	Comments	Comments from the authors
		validation in 60+ of the pain/ADL measure (ZBPI)) – see comments in Appendix 1and in page 11 – lines 26-29. See A0005 – page 73 lines 36-57.	provided which may lead to another conclusion about pain assessment. See also above about page 11 line 26-29.
11	49-50	Refer to previous comments page 11 – lines 15-17: remove 'no' and replace by 'limited' data exist on immunocompromised groups.	Changed to: little to no information
11	37-52	We strongly suggest that the conclusion : - encompasses the 4 domains of the REA, and to conclude as well on the health problem, patient & society burden - mentions the evidence and results of real-life effectiveness	See previous comment on how conclusions are presented in the rapid REA. Therefore, no changes will be provided.
16	30-32	Please add: Criteria used in the SPS corresponds to RCT condition, i.e. provides high-level quality of diagnosis confirmation. This is strength of the RCT as only confirmed cases were kept in further analyses. Johnson et al 2007 (reference 19 of MAH submission file) report that up to 20% of clinical diagnoses are incorrect.	Paragraph has been integrated with: Criteria followed in the Shingles Prevention Study [Oxman 2005] appear to be uncommon in real clinical practice. DNA is not always also extracted from clinical specimens obtained from participants suspected of having HZ. Data of Johnson 2007 are now reported in A0024 and on page 18 of the final report (page 16 of the concept). The following text has been added: The condition that is most commonly mistaken for HZ is herpes simplex virus infection (see A0024).
16	45	End of the sentence is missing.	Text has been changed.
16	51	Add more detail on burden on patient and on society from A 0005 for HRQoL and ADL (see comment page 6 – line 19).	The following text was added:" HZ and PHN have a negative impact on the physical, psychological, functional and social status of patients. Pain is one of the main symptoms of PHN and has both for HZ and PHN a major impact on perceived quality of life. Pain and anxiety are the dimensions of the EQ-5D that are most affected by HZ. (A0005)".
17	3-4	Mortality data from EU countries other than NL have been provided in the MAH submission file – pages 25-27 (references 99, 100, 102 – WHO database; van Hoek,	Text has been changed.

Page	Line	Comments	Comments from the authors
		2009, JCVI statement 2010).	
17	29	Conflicting wording with p 7 line 14 : keep wording of the page 7 and correct page 17 that in few cases the therapy is started within or after 72 hrs.	Text has been reworded as follows: "In a few cases, the therapy is started more than after 72 hours of the onset of acute symptoms because the patient delays the medical visit or the, often unusual, symptoms of the disease have made diagnosis difficult for the physician. Current treatments for PHN are tricyclic antidepressant drugs (TCAs), alpha-2-delta-ligands, opioids and topical agents. Aciclovir, valaciclovir, famciclovir [Schmader 1999; Sacks 2013] and brivudin have also been used to treat PHN. At the moment, antiviral drugs are not approved for PHN, only for HZ treatment."
17	32	Effect on prevention of PHN has been removed from antivirals' indication in 2012, so please remove this part of the sentence – keep consistency with page 7 line 18-19.	Sentence has been reworded as follows: "Current treatments for PHN are tricyclic antidepressant drugs (TCAs), α-2-δ-ligands, opioids and topical agents. Aciclovir, valaciclovir, famciclovir [Schmader 1999; Sacks 2013] and brivudin have also been used to treat PHN. At the moment, antiviral drugs are not approved for PHN, only for HZ treatment."
18 & 19	20-24 & 32-33	Other real life data exist: - On the US programme: please consider references 187 & 188 of the MAH submission file: Hampton 2008 and CDC 2011NHIS survey - Effectiveness: please refer to Tseng et al jama 2011 (refer to pages 101 – 103 of MAH file)	Data of the real life studies has been presented in D0017.
18	33 table	Target population recommended and funded in the UK is ***70-79*** (instead of 70+) – well-described in page 22.	Changed.
19	3	This is logical in a clinical study to rule out misdiagnosis. Has nothing to do with real clinical practice. See comment page 16 – lines 30-32.	We only stated the difference between RCT and daily practice. We interpret this comment as confirmation.

Page	Line	Comments	Comments from the authors
19	41	Therefore there might be an underdiagnosis in real life and thus higher incidence rates.	Paragraph has been adjusted and reworded as follows: The method followed for HZ diagnosis. Criteria followed in the SPS for HZ diagnosis appear as quite uncommon in real clinical practice. DNA is not always extracted from clinical specimens obtained from participants suspected of having HZ. A wrong diagnosis complicates the interpretation of the results.
19	23-24	Precise that: The initial registration on 19 May 2006 was for the frozen formulation and refrigerated form was approved in January 2007.	This has been changed.
19	41-42	See comments page 19 - lines 3-4.	Duplication has been eliminated.
19	46	Precise (or remove?) why attention should be paid to decisions belonging to the countries. Unclear.	The bullet point has been removed.
21	4	Please refer Gilderman letter to the editor Clinical & Vaccine immunology 2009 (new reference attached): Concerning the choice of immunologic assay and the rationale for using the gpELISA as a serological marker for immune response to Zostavax, is based upon the SPS CMI substudy. ***gpELISA may reflect a "downstream" measure of the CMI response to ZOSTAVAX and constitute an appropriate assay for RCTs evaluating the comparability of vaccine formulations, concomitant administration with other vaccines and use in certain subgroup populations.***	See our response to previous comment (p.11 lines: 10-14).
21	14	Please complete the sentence: …minimum potency of 19,400PFU, which corresponds to the minimum potency at expiry (end of shelf life), therefore, higher potencies are necessary at release of the lots (to take into account potency loss within the 18 month-shelf life time).	Text was added at pag.21 as well as in B0001 card and in the Applicability table. In the Applicability table the following text has been added: “EMA requires that 1 dose (0.65 ml) of Zostavax contains a minimum of 19,400 PFUs (plaque forming units), which corresponds to the minimum potency at expiry (end of shelf life).Higher potencies are necessary at release of the lots to take into account potency loss within the 18

Page	Line	Comments	Comments from the authors
			month-shelf life time".
21	15-16	Please reword as lots with various potencies have been tested as part of the clinical development of ZOSTAVAX. For example, in the SPS, 12 clinical lots of zoster vaccine were used, 9 of which were heat treated to accelerate aging of the vaccine. Potency upon shipment to study sites ranged from 21,000–62,000 PFUs/dose, but potency and accelerated aging did not significantly influence vaccine efficacy with regard to zoster, PHN, or BOI. Refer to reference 4 of the MAH submission file – CDC 2008; Arnou 2011 (reference 245 MAH file) confirmed that ZOSTAVAX refrigerated formulation elicited acceptable immune response in ≥50 y of age when stored as directed and administered during the 6 months prior to expiration. Supportive evidence from an integrated analyses of immunogenicity (based on 8 RCTs - confidential) as well as Arnou et el 2011 led the EMA CHMP to cancel a FUM of lots comparisons in Oct 2010 – MAH file page 120.	Text has been reworded as follows: Detailed information needed to investigate the dose-response relationship and duration of protection of the vaccine was not available (B0001).
21	38	Correct: Pregnancy should be avoided for ***one month*** following vaccination. (see EU SPC).	Text has been modified according to the suggestion.
22	7	One word is missing: HZ ***vaccine*** adverse events.	This has been corrected in the text.
22	25 26	For potency – refer to comment page 21 line 15-16. In ***efficacy*** clinical trials – indeed refrigerated forms has been studied in other RCTs (immunogenicity & safety), notably the bridging study supporting the EMA variation in 2007..	Text has been rewarded as follows: "Differences between the approved formulation (refrigerated and with a minimum vaccine potency of 19,400 PFU) and the formulation of Zostavax studied in the pivotal clinical trials. In pivotal clinical trials the frozen formulation and a potency ranging from 18,700 to 60,000 PFU were studied. Despite the bridging study, the effect of the refrigerated formulation on relevant outcomes, such as prevention of HZ or PHN, has not been studied." The reference to the bridging study has been inserted and is discussed later.
22	29	***Off*** label use?	This has been changed in the text.
22	19	Remove 'from 2014' as this refers to internal manufacturing plans – not for broad	This has been reworded according to the

Page	Line	Comments	Comments from the authors
	& 34-35	public disclosure. Manufacturer is Merck whereas sanofi pasteur-MSD is MAH in Europe. Change sentence to be: ***"Significant investments have been made by the producer (Merck) on manufacturing, which should allow more supply of ZOSTAVAX worldwide, especially in Europe."*** (no date to be mentioned). See comment in B0003.	suggestions of the MAH.
24 & 25	18-20 & 43	It is not concomitant administration of ZOSTAVAX and corticosteroids. But ***administration of ZOSTAVAX in patients treated with chronic/maintenance corticosteroids*** (<20mg/day eq prednisolone).	Reworded.
24	General	Reorganise by study source for clarity (mix between SPS and ZEST misleading in the current version). Suggestion to provide data on vaccine-related SAE (see SmPc section 4.8. providing number of vaccine-related SAE for SPS and ZEST).	It is not clear to us which part of the text is misleading. Therefore we see no reasons for the changing the presentation of the text. In the first sentence of the main results can be read: 'In the clinical studies, the overall incidence of vaccine-related injection-site adverse reactions was significantly greater for participants vaccinated with Zostavax (frozen formulation) compared with those who received placebo (48% versus 17% in the SPS Substudy and 64% versus 14% in the ZEST study).' These percentages are also presented in the SPC of Zostavax under section 4.8.
24	49	Application should be replaced by ***administration*** (of the vaccine).	Changed.
24	49-52	Regarding the risk of allergic reactions, need to add that after further review of the medical records, more than 80% of the events involved localized inflammatory response with various degrees and combinations of redness, swelling and/or tenderness at the site of the injection … see Tseng Journal of Internal Medicine, 2012 (reference 209 in MAH submission file).	A sentence has been added.
25	3	"No new clinical studies.." ? It contradicts with the 12 ongoing studies – refer to page 8 line 23.	Text has been reformulated as follows: "No new clinical studies are planned by the manufacturer for this specific age group of 50-59 years old."

Page	Line	Comments	Comments from the authors
25	8	Suggestion to replace "otherwise not ill" by ***"healthy".***	Persons who are otherwise not ill are not per se healthy. In the elderly population, co morbidities (which may be well controlled) are frequently seen. Suggestion will not be taken over.
25	9	Please specify what is meant by 'long-term' as safety data from US exist from 10+ years already.	This has been already mentioned on line 1 of the same page.
25	44-45	First results in HIV patients on ART described in MAH submission file (page 99 – reference: http://clinicaltrials.gov/ct2/show/NCT00851786.	A sentence has been added: A clinical trial with hiv patients is ongoing.
25	47-49	Suggestion to a add "respectively in 60+ (SPS) and 50-59 (ZEST) age groups"	This paragraph has been rephrased, information about different age groups has been added.
26	9	These are the most likely vaccines in these age groups.	It cannot be excluded that other vaccines (such as vaccination for travelling) can be used in these age groups.
26	13	see comment above: First results in HIV patients on ART described in MAH submission file (page 99 – reference: http://clinicaltrials.gov/ct2/show/NCT00851786.	The specification of hiv patient has been removed. The sentence is now general for immune-compromised individuals.
28-29	general	Real life effectiveness studies (Tseng et al jama 2011, Langan PLoS medicine 2013) should be added in these parts (VE hospitalization, VE HZ, VE PHN).	Data of the real life studies has been presented in D0017.
29	25	Note on VE for 50-59: Note that VE HZ you present in the table is not that of the EU SPC: you mention M-ITT (72%), while EU SPC is referring to ITT (70%). Note: BOI in ZEST refers to 21 days (and not 90 days as in the SPS) – see comment page 10 table.	We choose to report the mITT data of the ZEST because data of the SPS is also mITT. The difference in the BOI definition is marked in the note (∫) below the table.
29	42	Add: ***Because, in the SPS, VE against HZ decreased with age (from 64% among subjects aged 60–69 years to 38% among subjects aged ≥70 years) and the VE against PHN remained constant with age (66% among subjects aged 60–69 years and 67% among subjects aged ≥70 years), additional VE against PHN would be expected to be age dependant. Therefore, an age-stratified analysis is necessary to accurately examine whether HZ vaccine reduces the incidence of PHN beyond the reduction in PHN incidence provided by preventing HZ. Results***	The text in the summary about VE PHN has been rewritten slightly after editorial review. Results of the studies were presented as such. According to these data, age dependency cannot be conclusively proven. There is also insufficient evidence available to state that an age dependency of the

Page	Line	Comments	Comments from the authors
		clearly reveal that, although there was no significant additional efficacy in preventing PHN in subjects aged 60–69 years, the vaccine efficacy in preventing PHN among subjects with herpes zoster who were aged ≥70 years was 49% (p=.01). The vaccine efficacy in preventing PHN among subjects with HZ who were aged ≥70 years remained statistically significant (reference 223 of the MAH submission file – Brisson 2007). Confirmed by reference 2012 of MAH submission file - Oxman, Human Vaccines 2007, also mentioning that: ***the ≥70 year old age stratum accounted for 71% of the cases of PHN in the SPS***". See comment page 8 – lines 42-45.	effect on PHN can be expected. Therefore, the textual suggestions will not be taken over.
29	50-51	Highlight ***main limitations of Chen Cochrane review:*** - Analyses differ from the primary analyses defined in the SPS protocol as the definition of the PHN has been modified (Pain persisting or appearing more than 4 months after onset of HZ rash instead of 3 months in the study protocol). The definition from Chen was indeed an alternative cutoff used to define PHN in sensitivity analyses. In Oxman, 2005, VE on incidence of PHN was also presented using alternative cutoff times for the duration (persistence) of pain, with VE PHN 68.7% (CI 45.2- 83.0) at 4 months and 72.9% (CI 42.1- 88.6) at 6 months (Table 3 p 2279 in Oxman, 2005 – MAH submission file page 81). - No stratification by age in Chen preventing any conclusions on the age-related effect of ZOSTAVAX on PHN prevention (see comment above). Refer to page 101 – MAH submission file – same comment page 156 lines 10-29	The difference in definition of PHN was already mentioned in the text. The issue here is about the effect of PHN beyond preventing HZ. The numbers SPMSD referred to is among all subjects.
29	55	Efficacy in reducing `***the occurrence of***` PHN.	Changed.
30	49-52	***Long term persistence study (LTPS) provided 10-year efficacy*** data that are incorporated in the SPC (refer to EMA SPC + MAH submission file page 87-89) – paragraph should be re-written as 10 year data were available at time of pilot REA writing.	There is no data on 10-years efficacy published. The text is correct. After editorial review, the text is slightly changed and reworded as: vaccine efficacy persists for at least 7 years.
31	1	***Refer to primary data ie Oxman 2005 & Schmader 2007*** instead of Gagliardi Cochrane. Indeed Gagliardi did not access to primary data as Oxman & Schmader did providing strongest analyses than a review.	Data from the Oxman study has been added.
32	39-40	SPS study has been designed using the BOI as the primary criterion as reported by Oxman 2005, although, it is to be noted that the protocol used for regulatory activities (e.g. FDA and EMA) included the incidence of PHN as a co-primary	The text has been reworded. It is mentioned that the incidence of PHN is a secondary outcome.

Page	Line	Comments	Comments from the authors
		endpoint and therefore the sample size for the overall population (60+) is appropriate.	
32 & 33	41-54 & 1-12	Please implement comments done in page 11 accordingly.	The text has been revised according to our responses to previous comment (p.11)
APPENDIX 1			
44		Selection of evidence should be justified, based on the presentation of the full clinical plan available for the technology. We suggest to present briefly the full clinical evidence of Zostavax (9 studies pre-licensure, and 16 post-licensure, including real-life experience), in order to provide an accurate view to EUnetHTA members (please refer to MAH submission file – from page 73) & (reviewed also in Clinical Effectiveness cards). As per REA guidelines, data from real life conditions (eg effectiveness) should be considered: add Tseng et al Jama 2011 & Langan et al 2013 (references 236 page 101&102 &complement of MAH submission). For RCT, data on short and long term persistence studies are also key evidence to consider in REA.	The text in the summary about VE PHN has been rewritten. An appendix has been added about the clinical development of Zostavax. In this table we have discussed the pivotal studies and the review articles. Real life data have been addressed in D0017.
48 table		Apply comment from page 8 – line 23. Change to: Twelve ongoing RCTs (i.e. CSR not yet available), add studies NCT01391546 – intramuscular versus subcutaneous administration route: immunogenicity & safety of ZOSTAVAX http://clinicaltrials.gov/ct2/show/NCT01391546?term=NCT+01391546&rank=1 & NCT00851786 - HIV-Infected Adults on Antiretroviral Therapy: immunogenicity & safety of ZOSTAVAX http://clinicaltrials.gov/ct2/show/NCT00851786?term=HIV+%26+zostavax&rank=1	NCT01391546 and NCT0085178 have been added to the table of ongoing studies.
59	1-2 & footnotes 5 & 6	Both pain severity and ADL have been measured by ZBPI, questionnaires specifically developed, adapted and validated in HZ subjects aged 60 and more (3 focus groups – see Coplan J Pain 2004 (reference 112 of MAH submission file). Remove your footnotes 5 & 6 & reconsider assessment of risk of bias (currently rated as H).	Our comments on the methodology are mentioned in the report. Some textual adjustments have been made in footnote 5 and footnote 6. Based on our evaluation, we consider the classification of high risk for pain severity and for ADL as appropriate.
59	Footnot	SAE is not defined in detail in Schmader 2012 as refer to guidelines from EMA & FDA (same as for SPS). Please find below the extract from ZEST protocol for full	The risk of bias for the SAE in the ZEST has been changed to low. The footnote is still

Page	Line	Comments	Comments from the authors
	e 9	definition: "In ZEST study, A serious adverse experience was defined as follows: A serious adverse experience is any adverse experience occurring at any dose that: † Results in death; or † Is life threatening (places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred. [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]); or † Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or † Results in or prolongs an existing inpatient hospitalization (hospitalized is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation.) (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience); or † Is a congenital anomaly/birth defect (in offspring of subject/patient taking the product regardless of time to diagnosis); or ALSO: Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the (†) outcomes listed above. In addition, Merck & Co., Inc. requires the collection of the following: cancer, or overdose (whether accidental or intentional). Remove your footnote & reconsider assessment of risk of bias (currently rated as H) which should be aligned on SPS.	needed to clarify that this cannot be found directly in the publication itself, but in the supplementary appendix and in the clinical protocol of the study.
60	Table 6	Could you explain why risk of bias are rated High for: - Incidence SPS & ZEST: selective outcome reporting unlikely (no) (5th column) and risk bias – outcome level (last column). - Pain SPS & ZEST: risk of bias – study level (2nd column).	- The explanation is put in the note below (note 10): PHN is pain related; pain assessment is a patient reported outcome. Therefore, we classify it as high risk. - The risk of bias on study level is based on several parameters as mentioned in the table. The lacking of blinding, the risk of

Page	Line	Comments	Comments from the authors
			selective outcome report, risk of bias on outcome level lead to a conclusion of high risk on study level.
61	Table cell on Population	Population: - Subgroup analyses for ≥80 yrs have been provided in MAH submission file and in references Levin, 2012 & Frazer 2011 – references 195 & 196 of MAH file) - Real-world data are also reported in Tseng et al. Jama 2011 for the 60+ population (Kaiser Permanente database) – see page 101-102 of the MAH submission file – reference 236. Should be added to Langan 2013.	The following information has been added :" Data of 80+ is provided by MAH". Real world data references have been mentioned as follows: "Real world data is reported in [Langan 2013, Tseng 2011]"
62	Table Cell on intervention	Potency: Please refer to comment page 21 – lines 15-16	Potency: The following text has been added in the Applicability table:" EMA that 1 dose (0.65 ml) of Zostavax contains a minimum of 19,400 PFU (plaque forming units), which corresponds to the minimum potency at expiry (end of shelf life).Higher potencies are necessary at release of the lots to take into account potency loss within the 18 month-shelf life time".
		HZ detection criteria: Please refer to page 16 lines 30-32.	HZ detection criteria are reworded: DNA is not always extracted from clinical specimens obtained from subjects suspected of having HZ.
		Expired vaccine: These data come from PSUR 02-May-2012 to 01-Nov-2012 and are confidential. Please delete them. Also ADRs due to expired drug administration do represent only 4% (169/4001) of the total number of ADRs for this review period. 19% correspond to the percentage of Expired drug administration in the category "Injury poisoning and procedural complications". For this reason we do not think that there is any significant risk of inappropriate use of Zostavax.	Expired vaccine has been reworded: Professionals (doctors or nurses) should pay attention to vaccine expiry date in order to avoid inappropriate use of the vaccine. Data from the PSUR has been removed.
62 & 63	Table cell on outcome	What about outcomes on incidence of HZ & PHN? Should be added.	The aim of the applicability table is to assess whether there is a relevant effect modification when a specific intervention is applied to the population of interest. No relevant effect was identified for as the incidence of HZ&PHN. Therefore they were not mentioned in this table.

Page	Line	Comments	Comments from the authors
		Suggestion to replace "otherwise not ill" by "healthy". Long term: please mention >10 years (as data for up to 10y exist and are in the EU SPC).	"Otherwise not ill" is not considered the same as "healthy". No modification to the text has been done. Long term: A further sentence has been added: "A study of long-term persistence of efficacy for up to 10 years post vaccination was conducted as part of pharmacovigilance activities required by EMA."
APPENDIX 2_CARDS A			
64	25	Add "therefore almost all European adults is VZV-positive and at-risk of HZ" (see MAH submission file pages 18-19)	It has been reworded as follows: "VZV is a herpes virus that causes two distinct diseases: varicella and HZ. The first usually occurs in childhood and is highly contagious [Guenther 2006]. Because almost all European adults are VZV-positive they are potential at-risk to develop HZ."
66	18-21	Unclear: interest of serologic testing? In which objective? Please clarify or remove	Text has been removed.
66 & 67	21 (table) & 36-37	Table mixes risk factors of HZ, risk factors of PHN and complications of HZ – please revise accordingly: - Prodromal neuralgia = risk factor for PHN (Johnson, 2007) - HZO may be a risk factor for stroke (Lin, 2010) - Bacterial infections = complications of HZ (Johnson, 2007)	Risk factors of HZ have been revised.
69	34-36	Suggest rewording to clarify both rash and pain symptoms: 'Although the rash is the most distinctive feature of HZ, the most frequently debilitating symptom is neuropathic pain which may occur during 3 time periods' […prodromal/subacute, acute, chronic] (source: Johnson et al, 2007 – reference 19 of the MAH submission file) – see page 6 line 13 (PHN is not acute…)	This has been reworded.
71	8-10	Suggest rewording to clarify both rash and pain symptoms: 'Although the rash is the most distinctive feature of HZ, the most frequently debilitating symptom is neuropathic pain which may occur during 3 time periods' […prodromal/subacute, acute, chronic] (source: Johnson et al, 2007 – reference 19	This has been reworded.

Page	Line	Comments	Comments from the authors
		of the MAH submission file) – see page 6 line 13 (PHN is not acute…) – see previous comment as well	
71	11	There is no agreed definition of PHN in the scientific community esp. regarding to the time at which HZ-associated pain become PHN and whether pain intensity should be included. However, consistent with recent data and concepts, current research trends to define PHN as significant pain persisting for 3-4months after rash onset, with pain score ≥3 on a VAS. (refer to MAH submission file ref 19 – Johnson et al 2007) This is also the reason why in the pivotal SPS (Oxman, 2005), clinical endpoint on PHN was "pain persisting or occurring at 90 days after the rash onset with pain score ≥3. ⇨ Please reword text accordingly to include 3-4 months PHN definition. This will also be consistent with what is written on A0002 page 65 lines 1-2-3 and country-specific figures (A0006) – comment page 6 – lines 18-19	This has been reworded.
87	12	The setting of the Brisson study is missing (Canada ?)	This has been reworded. Brisson is mentioned for UK (the title of reference is Epidemiology of Varicella-Zoster Virus in England and Wales).
90	41	Typo: $?	Typo has been eliminated.
94	9-12	Refer to specific answer from the MAH attached to the comments (Annex 1): Further investigations have been performed by Sanofi Pasteur-MSD to answer to EUnetHTA request, accessing to Dutch data (refer to in the MAH submission file dated 12.04.2013), German and Italian data. Proportions are presented below and are quite consistently showing that the **proportions of people to exclude from ZOSTAVAX vaccination, due to contraindications are comprised between 7% and 11% of the ≥50 years in European countries.** All these figures give estimates of what could be the population non eligible for ZOSTAVAX vaccination, knowing that even if immunocompromised, some of them may receive ZOSTAVAX under certain condition, on a case by case basis after seeking appropriate specialist medical advice.	This has been changed as follows: "According to published studies [Gialoretti 2010, Schiffner-Rohe 2009] and SPMSD estimates, proportions of people to exclude from ZOSTAVAX vaccination, due to contraindications are comprised between 7% and 11% of the ≥50 years in European countries"
95	1-8 &	More than 1 study provides evidence on the use of the technology in the US – refer to MAH submission file pages 50-51 >13.6 M doses used worldwide and coverage rates in US have been published (ref	Langan and Tseng have been reported in A0011. Discussion has been reworded as follows: "

Page	Line	Comments	Comments from the authors
	9	187 & 188: CDC 2011 & Hampton 2008) Revise accordingly please.	Two published studies reported real life data on a HZ vaccination program conductec in the USA [Langan 2013] [Tseng 2011]. Vaccine uptake was low in [Langan 2013] (3.9%) especially among older people (>80 years old), while in [Tseng 2011] a higher rate of uptake emerged (25%) especially among older people (>80 years old). Women and immunosuppressed people were more likely to take vaccination [Langan 2013]. The low uptake in the USA may be related to the problems with the production of the vaccine and the storage problems for the frozen version of the vaccine".
97	39-40	Replace 'is' by 'may be' , indeed prodromal phase is not observed in all HZ cases.	This has been reworded.
100	47-50	Unclear paragraph – varicella & children are out of the scope of present REA.	This paragraph has been removed.
103	13-15	Precise that EMA authorisation on 19 May 2006 was for frozen formation (refrigerated approved in January 2007).	This information has been added.
104	36 Table	UK: change covered population is 70-79 (and not 70+).	This has been changed in the text.
106	25	Last sentence should be copy-paste in Austria paragraph (not UK).	This has been adapted according to the suggestion.
106	44-47	Correct information is as follows (important to put things in context): In 2006, France did not consider the inclusion of HZ vaccination among elderly because data on effectiveness among elderly was considered to be insufficient at time of evaluation.	This has been reworded.
APPENDIX 2_CARDS B			
109	12	Suggest adding the approved population: adults 50+ immunocompetent and specify that no need to check VZV status (VZV seropositivity or history HZ) prior vaccination with ZOSTAVAX. See EU SPC.	The text has been modified as follows: "Zostavax is a lyophilized preparation of live, attenuated varicella-zoster virus (Oka/Merck strain), containing the same strain as in the vaccine against VZV-primo-infection (chickenpox). it is intended to be

Page	Line	Comments	Comments from the authors
			used in VZV-seropositive immunocompetent adults (≥ 50 years old). To administer Zostavax, there is no need to check on the VZV status in terms of VZV seropositivity or history of HZ or prior vaccination with Zostavax."
110	7-15 & 34-43	Refer to comment page 11 – lines 10-14 and to comment page 21 – line 4.	See response to comment 11 (10-14).
111	General B0002	It should be not that therapeutic indication of ZOSTAVAX differs from one country to another. - Prevention of HZ: eg in the US and Canada: http://www.merck.ca/assets/en/pdf/products/ZOSTAVAX-PM_E.pdf - Prevention HZ and prevention of PHN: eg. Europe - Prevention of HZ, prevention of PHN and reduction of acute and chronic zoster-associated pain; eg. in New Zealand: http://www.ncirs.edu.au/immunisation/fact-sheets/herpes-zoster-vaccine-fact-sheet.pdf	EMA and FDA indications had already been reported in B0002. A sentence on New Zealand has been added. The following sentence has been added in B0002, at the discussion section: "Apart from those authorization details, no other differences emerge at country level, as far as indications of use of Zostavax are concerned."
112	17	Pregnancy should be avoided for one month following vaccination (not 3 months- please refer to EU SPC).	This has been reworded.
113	16-17-18	Please correct as follows: More recently, doses have been made available in limited quantities in the UK ***as part of the NHS reimbursement in 2012*** (refer to MAH submission file page 51). There is no link between the availability of the doses in 2012 and the National Immunisation plan.	The sentence has been removed.
113	21-22	***Remove 'from 2014'*** as this refers to internal manufacturing plans – not for broad public disclosure. + add reference to Gerberding 2012 (reference 189 of the MAH submission file).	This has been changed according to suggestion. The reference to Gerberding 2012 has been added.
113	25-26	Manufacturer is Merck whereas sanofi pasteur-MSD is MAH in Europe. Change sentence to be: "Significant investments have been made by the producer (Merck) on manufacturing, which should allow more supply of ZOSTAVAX worldwide, especially in Europe." (no date to be mentioned).	Sanofi has been changed to Merck Sharp& Dohme.

Page	Line	Comments	Comments from the authors
115	11	More than 1 study provides evidence on the use of the technology in the US – refer to MAH submission file pages 50-51. >13.6 M doses used worldwide and coverage rates in US have been published (ref 187 & 188: CDC 2011 & Hampton 2008. Revise accordingly please. Refer also to A0011 comment.	A paragraph on Tseng 2011 has been added.
115		The questions B0006 and B007 are missing while B0006 is referred to in page 113 line 18. Please correct accordingly.	B0006 and B0007 questions from the template were not included in this REA. The referral on page 113 has been corrected.
118	12-17	Mix of information: data on VE cannot be retrieved from Cost-effectiveness analyses which are supposed to be out of EUnetHTA scope. Congress (ICAAC/IDSA 2008) mentioned is out of date now that both EU SPC & publication are available. Please, remove and replace by stating that VE estimates are provided up to 10 years post-vaccination…. Please correct full paragraph to mention EU SPC on short term & long term efficacy + publication from Schmader et al. 2012 (reference 218 of MAH submission file – pages 87 to 89).	Congress (ICAAC/IDSA 2008) was reported to present information on the approval process. Text has been modified as follows: Long-term efficacy data were for the first time presented at ICAAC/IDSA 2008. Data from the SPS trial concerning vaccine efficacy for HZ cases and BOI by year after vaccination, were presented for up to 10 years.
118	18-20	These data come from PSUR 02-May-2012 to 01-Nov-2012 are confidential. Please delete them.	As indicated before all information that is mentioned in the submission file could be used for citation as noted in the scoping notes. Therefore, no change has been made.
118	29-30	The sentence concerning the RMP update is confidential.	See previous comments.
120	36	Greece: not fully decided yet (to MAH knowledge).	This has been reworded.
APPENDIX 2_CARDS C			
122	21	Suggestion to add "including the SPS and the ZEST study with more than 22 000 adults 50-59 years old.	The numbers of the ZEST have been added.
122-125		Check tables ref numbers + check the structure of presentation study by study (tables versus texts).	These suggestions are unclear and will not lead to any changes in the text.
126	37-40	See comment above – preliminary results available for HIV patients.	It was mentioned in the paper that a clinical trial (NCT00851786) was on-going. Data were presented on a conference, but there are currently no data published in a peer-

Page	Line	Comments	Comments from the authors
			reviewed journal to which can be referred in this report.
126		Please add: - Safety related to administration of Zostavax with prior herpes zoster (see Zostavax SmPC page 6 and Mills et al 2010).	The following paragraphs have been added: *[Mills 2010]* Safety, tolerability, and immunogenicity of zoster vaccine in persons with a history of HZ; n=101;, participants ≥50 years of age; follow up: 28-days. No serious AEs were reported within the 28-day safety follow-up period. The proportion of participants reporting systemic AEs was similar in both arms.Two vaccine-related systemic AEs were reported in participant following administration of zoster vaccine: pain and myalgia of moderate intensity; and axillary pain of mild intensity. The rate of reported injection-site AEs was higher in vaccine recipients (45.9%) than in placebo recipients (4.2%). One varicelliform rash was noted in both the HZ vaccine group and the placebo gropu. The most frequently reported injection-site AEs in vaccine recipients were erythema (33.7%), pain (36.7%), and swelling (26.5%).

Page	Line	Comments	Comments from the authors
		- Safety on refrigerated form versus frozen has been assessed in the "bridging study" (see Gilderman at al 2008).	*[Gilderman 2008]* Immunogenicity study of a refrigerator-stable formulation of Zostavax; n=368; participants ≥ 50 years; follow-up: 28 days. Clinical AEs were reported at a lower rate by the recipients of the Zostavax refrigerated formulation than by the recipients of the Zostavax frozen formulation. The most frequently reported injection-site AEs (10% in both vaccination groups) were erythema, pain, and swelling. The incidences of systemic clinical AEs were similar in both vaccination groups, with 6% determined to be vaccine related in either vaccination group. One non-injection-site varicella-like rash with three lesions was reported by on subject in the Zostavax (refrigerated form) group. No subject discontinued the study due to an AE."
131	14	Same comment as above: Regarding the risk of allergic reactions, need to add, as stated in the publication (Tseng Journal of Internal Medicine, 2012 – reference 209 of MAH submission file) that after further review of the medical records, more than 80% of the events involved localized inflammatory response with various degrees and combinations of redness, swelling and/or tenderness at the site of the injection.	The following sentence is added: "The medical records of patients who were reported as having an allergic reaction (n=118) were objected to a further review. Of the 71 patients whose medical visit was determined to be the result of a reaction to the zoster vaccine, most (n=59, 83%) complained of a localized inflammatory response with varying degrees and combinations of redness, swelling and/or tenderness at the site of the injection. Eleven (15%) presumably allergic, pruritic, urticarial, macular or papular rashes were described. A single patient was described as having a zosteriform rash a few hours after getting the shingles vaccine.".
132	2 - 6	These data come from PSUR 02-May-2012 to 01-Nov-2012 are confidential. Please delete them.	As communicated before (see also the document summary of the scoping

Page	Line	Comments	Comments from the authors
			meeting): it should be possible to cite from the submission file for the purpose of drawing up the report. Given the relevance of the topic (safety in the oldest elderly) we should be able to cite from submission file.
133	10	Suggestion to delete 'treatment' as Zostavax is not a treatment but a vaccine (same for placebo).	The word “treatment” has been removed.
134	20 -23	Same comment as above: Regarding the risk of allergic reactions, need to add, as stated in the publication (Tseng Journal of Internal Medicine, 2012 – reference 209 of MAH submission file) that after further review of the medical records, more than 80% of the events involved localized inflammatory response with various degrees and combinations of redness, swelling and/or tenderness at the site of the injection.	The following text has been added: “Among those cases, more than 80% of the events involved localized inflammatory response with various degrees and combinations of redness, swelling and/or tenderness at the site of the injection ”
135	39 -40	These data come from PSUR 02-May-2012 to 01-Nov-2012 are confidential. Please delete them.	Please see our prior comment.
136	1	These data come from PSUR 02-May-2012 to 01-Nov-2012 are confidential. Please delete them.	Please see our prior comment.
136	26	Suggestion to replace "otherwise not ill" to "healthy".	In our opinion ”otherwise not ill” is not the same as “healthy”.
140	22 to 25	These data come from PSUR 02-May-2012 to 01-Nov-2012 are confidential. Please delete them.	Please see our prior comment.
140		Data concerning study on chronic steroids treatment are missing.	The EMA has already come to the conclusion that 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. For the completeness new text has been added.
140	26	Replace SPC by SPS.	Changed.
140	34	Following observed differences in terms of results in the SPS safety substudy and the SPS, a general safety study of zoster vaccine (ZV) in adults ≥60 y old was performed with follow up for serious adverse experiences (SAE s). ZV and placebo	A sentence has been added: In the study of [Murray 2011], the relative risk for SAE for subjects ≥ 80 years old is comparable

Page	Line	Comments	Comments from the authors
		groups had similar safety profiles in terms of SAEs (Cf Murray Human Vaccines 2011 – reference 210 of MAH submission file).	between the ZV group and placebo group.
141	14 to 15	Replace 'fulnerable' to 'vulnerable'. Also study published in Baxter, 2012 – reference 211 of MAH submission file) provides safety data on the age group over 80: over 29000 subjects included in this study, among them more than 3200 over 80 (11%). In the sub-cohort of people who were 80 years of age or older, non-traumatic joint disorder was the only Health Outcome with an increased RR.	Typo has been corrected. The major findings of this observational study of Baxter are added in the results section of C0005.
APPENDIX 2_CARDS D			
149	general	It should be reminded that in both SPS and ZEST studies it was specified in the protocol that the physician have to offered to subjects with HZ, an antiviral drug and standard-of-care treatment for pain. Pain management was not specified in the study protocol and was chosen by the physician, as done in routine condition. In the SPS, the rate of use of antiviral medication among subjects with confirmed cases of HZ was similar in the two groups (87.3% in the vaccine group and 85.7% in the placebo group), as was the proportion in whom treatment was initiated within 72 hours of the onset of rash — in 64.1% in the vaccine group and 65.9% in the placebo group. The frequency of use of various medications to treat pain resulting from HZ was similar in the two groups, and the average duration of the use of opioids and the average quantity of opioids used among subjects with HZ were greater in the placebo group than in the vaccine group. Thus, differences in the use of pain medication did not inflate the estimates of VE BOI or VE PHN. This suggests that the overall effect of the vaccine was in addition to any benefit that may have been obtained from timely medical therapy. (Oxman 2005, Schmader 2012 & Zostavax SmPC New Zealand http://www.ncirs.edu.au/immunisation/fact-sheets/herpes-zoster-vaccine-fact-sheet.pdf)	Specific data about the used co-medication is not available. Not only the amount of people using co-medication, but also the specific drug used, the prescribed dosage, adherence etcetera may be important parameters influencing the pain and progression of the disease. Without these data in detail presented, we cannot confirm the statement of the authors of the clinical trials.
149	28	BOI was primary endpoint only in SPS – in ZEST, incidence HZ was the primary endpoint. Please correct.	Corrected.
150	11	- Quality of body of evidence of VE BOI is rated as "low", when this level is not justified nor consistent with result cards D0002B2, D0005, D0006, D0011A&C in pages 159-163. We have provided in pages 83-84 of the MAH submission file the HZ severity-of-illness scores e.g. components of the composite endpoint: BOI. BOI was co-	In the results cards, we present data as answer to the question. Based on these (and other) findings we further discuss the topic in the main results and general discussion. The critics upon the use of this composite

Page	Line	Comments	Comments from the authors
		primary endpoint of the pivotal SPS with incidence of PHN, endpoints considered as valid by both EMA and FDA. Moreover, a specific method for assessing the combined effect on disease incidence, severity by duration weighted for age group was used (Oxman 2005 & Chang 1994). To address your concern we enclose a methodological note (Annex 2). Referring to your guidelines on "HTA Core Model for rapid REA", this note states that: • BOI is not the single primary endpoints of SPS • Number of components are limited to 2 (HZ incidence and severity-of-illness scores/AUC) • Justification that BOI is a suitable endpoint has been justified in Coplan, 2004 ; Chang, 1994; Oxman 2005	endpoint are presented in the discussion on page 11 and in several places in section 5.2 (main results). It is a logic conclusion consistent with the findings in the results card and our guidelines. The fact that the registration authorities have accepted BOI will not imply that it should be automatically accepted for the REA because the context of the assessment is different. In this case we are assessing the effectiveness and not the efficacy in accordance to the EUnetHTA guidelines, including the one on “Composite Endpoints”. The guidelines on REA were issued by EUnetHTA and made publicly available on the EUnetHTA website. In addition, it was indicated during the scoping meeting with MAH, that it was essential to take those guidelines into account for the description and assessment of the composite endpoints. Additionally it has to be mentioned that we do not agree with the statement that the number of components is limited to two: also the severity of illness score is a composite measure.
152	17-24	Presentation of Gagliardi finally confirm/repeat SPS results – which is logical as it is the only efficacy trial of the Cochrane => interest of such a paragraph?	The Cochrane review of Gagliardi includes more publications than only the SPS. Besides, Cochrane reviews synthesize data in a transparent and structural way resulting in high quality information. Therefore incorporating this publication is relevant. Confirmation of the results is also a finding.
153	3	Please provide ***VE HZ from ZEST*** (Schmader CID 2012 & EU SPC). + add ***real life effectiveness*** data Tseng 2011 & Langan 2013.	This section is referring to the age dependency of VE HZ. In Schmader 2012, no age specific efficacy can be found.

Page	Line	Comments	Comments from the authors
			Real life effectiveness is reported in D0017.
154	35	Add: ***due to the epidemiological features of PHN which occur more frequently after the age of 60 or even 70.*** (see comment in page 11).	The text has been expanded as follows: 'Because of the low incidence of PHN in participants aged 50-59 years old, the effect of Zostavax on the incidence of PHN was not studied in this age group.'
155-156		You can add: VE against PHN among subjest who develop HZ aged ***≥70 is: 47%*** (13-67%) ***source CAN or M as it is available in the latest SmPC (page 19) available at:*** http://www.merck.ca/assets/en/pdf/products/ZOSTAVAX-PM_E.pdf	Added.
156	4-9	- We suggest to copy/paste from page 29 line 40: ***"Overall, the VE PHN was 66.5% (95% CI: 47.5 to 79.2; P<0.001) as compared to the total population. There were no significant differences in the VE PHN when the results were stratified according to age".*** - Moreover, to explain this stable vaccine efficacy on PHN whatever the age , taking into consideration the vaccine effect in preventing PHN beyond its effect on the incidence of HZ, in relation to the age , as follows: ***"Efficacy for the prevention of HZ was highest among 60-69 and declined with increasing age. However, no significant differences among persons aged 60-69 versus these aged ≥70 years in vaccine efficacy at reducing PHN, probably because the independent effect of reducing PHN among patients who develop HZ was greatest among persons 70-79."***– see MAH submission file pages 92-93 & CDC MMWR, 2008 & Oxman, Hum Vacc 2007 p66. See also comments for page 8 lines 42-15 & page 29 line 42. - It should be noted that vaccine efficacy on PHN in the age group of 50-59 years old was not investigated as due to the epidemiological features of PHN which occur more frequently after the age of 60 or even 70.	The section is referring to information from the FDA leaflet. In that document the comparison in VE PHN towards the total population was not mentioned. So the suggestion will not be taken over. Description of the trend is already mentioned in the report elsewhere. The VE PHN towards the total population is reported under Oxman 2005 in this section. The age dependency of Zostavax in VE HZ is discussed in the section about incidence of HZ. There is no need to repeat it here. Under the handling of Schmader 2012, a sentence has been added: Because of the low incidence of PHN in participants aged 50-59 years old, the effect of Zostavax on the incidence of PHN was not studied in this age group.
156	10	Highlight ***main limitations of Chen Cochrane review:*** - Analyses differ from the primary analyses defined in the SPS protocol as the definition of the PHN has been modified (Pain persisting or appearing more than 4 months after onset of HZ rash instead of 3 months in the study protocol). The	There is already a note put in the report [Chen 2011 (Cochrane review)] to stipulate the difference in definition.

Page	Line	Comments	Comments from the authors
		definition from Chen was indeed an alternative cutoff used to define PHN in sensitivity analyses. In Oxman, 2005, VE on incidence of PHN was also presented using alternative cutoff times for the duration (persistence) of pain, with VE PHN 68.7% (CI 45.2- 83.0) at 4 months and 72.9% (CI 42.1- 88.6) at 6 months (Table 3 p 2279 in Oxman, 2005 – MAH submission file page 81). - No stratification by age in Chen preventing any conclusions on the age-related effect of ZOSTAVAX on PHN prevention (see comment above). Refer to page 101 – MAH submission file – refer to comment page 29 lines 50-55.	A sentence has been added: Also no data stratified by age has been presented.
157-158	8-13	As presented in the MAH submission file pages 83 & 84 (reference to EU SPC), evidence on the e***ffect of ZOSTAVAX on pain*** is the following: - Prevention of ***HZ cases with severe pain*** (score>600) in the overall population aged ≥60 years: ***73%*** (46-87%) - ***Among vaccinated subjects who develop HZ: significant reduction of the overall acute & chronic HZ-associated pain over 6 months:*** 22% reduction (p=0.0008) in the severity-by-duration score & 52% in the risk of having HZ with severe & long lasting pain (score >600). - ***Among vaccinated subjects who develop PHN: 57% reduction in the severity-by-duration score*** in the period from 90 days (after rash onset) to end of the follow-up (p=0.016). Sanofi Pasteur-MSD requests a revision of the judgement 'insufficient' regarding the evidence on pain. (See comment page 9 line 1).	As stated before, due to the complexity of the methodology, it is not feasible to show the collected data in a transparent way, independent of the covariates. As mentioned in the report, data about the pain assessment like the ZBPI is also a composite endpoint. According to the EUnetHTA guidelines, we must separate a composite endpoint to the individual parameters. Published data on these individual parameters is not available and therefore the judgment will remain 'insufficient'.
161		Please change title of column to ***'VE on proportion of PHN among HZ cases'*** see comment on table page 10.	Title of the column has been revised.
162	27	Add 'proportion of PHN among HZ cases" in title stating 'incidence of PHN'.	Title of the column has been revised.
163	5-16	Please implement comments done in page 29 lines 44-45. Add: ***Because, in the SPS, VE against HZ decreased with age (from 64% among subjects aged 60–69 years to 38% among subjects aged ≥70 years) and the VE against PHN remained constant with age (66% among subjects aged 60–69 years and 67% among subjects aged ≥70 years), additional VE against PHN would be expected to be age dependant. Therefore, an age-stratified analysis is necessary to accurately examine whether HZ vaccine reduces the incidence of PHN beyond the reduction in PHN incidence provided by preventing HZ. Results***	The text in the summary about VE PHN has been rewritten slightly after editorial review. Results of the studies were presented as such. According to these data, age dependency can not be conclusively demonstrated. There is also insufficient evidence available to conclude that an age

Page	Line	Comments	Comments from the authors
		clearly reveal that, although there was no significant additional efficacy in preventing PHN in subjects aged 60–69 years, the vaccine efficacy in preventing PHN among subjects with herpes zoster who were aged ≥70 years was 49% (p=.01). The vaccine efficacy in preventing PHN among subjectswith HZ who were aged ≥70 years remained statistically significant (reference 223 of the MAH submission file – Brisson 2007). Confirmed by reference 2012 of MAH submission file - Oxman, Human Vaccines 2007, also mentioning that: ***the ≥70 year old age stratum accounted for 71% of the cases of PHN in the SPS***". + limitations of Chen (see above comment).	dependency of the effect on PHN can be expected. Therefore, the textual suggestions will not be taken over.
163	27-43	Refer to comment on table page 10 and enclosed note on BOI.	Please see our response on the comment regarding the use of BOI. There is no new information provided that will lead to other point of view. Therefore the text will not be changed.
165	3 & 8	Error with CI (inferior band): change '5' by '='	Changed.
166	16-17	Please add real life data on VE concomitant administration PPV23 and ZOSTAVAX (Tseng et al 2011 – reference 231 and page 102-103 of MAH submission file).	Real life data have been presented in D0017.
166	19	Change 'will' by 'could' – refer to MacIntyre 2010.	Changed.
165	12	Add evidence coming from real-life effectiveness studies including immunocompromised conditions (AID) – Zhang Jama 2012 & Langan, 2013.	Real life data have been presented in D0017.
167	General for D0011	Currently, you focus only on RCT data, please consider real-life effectiveness: VE on hospitalisation: 65% (HR: 0.35 – CI: 0.24-0.51) among ≥ 60y but also by age ranges – source Tseng et al. jama 2011 – see MAH submission file page 102.	Real life data have been presented in D0017.
171	20	Mention that a long term effectiveness study (page 102 MAH submission file – reference 222 http://clinicaltrials.gov/ct2/show/NCT01600079.) will provide addition evidence on 10-year effectiveness from the age of 50.	This is a study that started in 2012 with an estimated completion date of 2023. This ongoing trial has been added to the reference list of this results card.
171	26	10-year VE are provided in SPC so please change the discussion accordingly (more than 7 years data are now available).	There is no data about 10-years efficacy published. The text is correct. After editorial review, the text is slightly changed and reworded as: vaccine efficacy persists for at least 7 years.

Page	Line	Comments	Comments from the authors
172	General	The calculation of NNV based on clinical trial (SPS) is limited as it includes the benefit of the vaccine during the duration of the clinical trial but not the benefits that can occur later. Therefore the time horizon considered by Gagliardi 2012 should be stated in line 39, and the limitations linked to the NNV calculation should be mentioned. The presentation of NNV was not included in MAH submission file. Other publications, based on modelling, present NNV. For instance, Brisson et al. 2008 (reference attached to these comments) estimated that for 65 year-olds, the NNV (HZ vaccine efficacy=63%, PHN vaccine efficacy=67%, no waning) to prevent a case of HZ, a case of PHN was 11 (90%CrI: 10-13) and 43 (90%CrI: 33-53) respectively. Results were sensitive to the duration of vaccine protection and the age at vaccination.	We agree with SPMSD that the calculation of NNV based on the available data is difficult and probably of limited value. Also the chosen time horizon was not specifically mentioned in the publication of Gagliardi 2012. Although the calculation of the NNV was included as a question in the project plan we decided to delete the NNV information from the report because of the mentioned problems with the calculation of the NNV and the limited value of NNV for this assessment.
173	29	Suggest to mention that ZBPI is a scale adapted from the Brief Pain Inventory to make it a HZ-specific measure of pain severity that captures pain and discomfort (including allodynia and pruritus) caused by HZ, validated for use in the population aged ≥60 years. (references Coplan, 2004; Schmader 2010 & Oxman, 2005 – pages 30 & 79 of the MAH submission file).	Comparable information is mention in the next sentence in line 35.
173	40	Please add as specify in Schmader, 2012: The Zoster Impact Questionnaire(ZIQ) was developed to ***rectify this deficiency.*** The ZIQ measures interference with 11 ADLs to measure interference with patients' ability or desire to put on clothing, bathe yourself, eat, groom yourself, travel, do shopping, do housework, prepare meals, get out of the house, participate in leisure activities, concentrate on mental tasks.'' ***Because the vaccine efficacy results for analyses using the ZIQ were similar to the results of analyses using the ZBPI, only the results using the ZBPI were presented*** in the publication.	A sentence has been added: The Zoster Impact Questionnaire (ZIQ) was developed to rectify this deficiency of validation in elderly people (≥ 60 year). According to the authors the data of ZIQ and ZBPI were similar, but these data were not shown.
174	49	Please add as specify in Schmader, 2012: Change in vaccine effect on ZBPI ADL Burden of Interference score with older age was assessed in general linear models including treatment, age, and an interaction term for treatment and age to test the significance of the change.	The ZBPI ADL Burden of Interference score is a complex and not transparent method to measure BOI. For that reason we do not feel that a linear regression of an outcome that is complex and not transparent has an additional value and should be mentioned in the report.
175-176	general	***Refer to primary data ie Schmader 2010*** instead of Gagliardi Cochrane. Indeed Gagliardi did not access to primary data as Oxman & Schmader did providing	Cochrane reviews are well established publication of high quality, based on an

Page	Line	Comments	Comments from the authors
		strongest analyses than a review.	independent assessments of research data. We believe that the Gagliardi paper provides an important systematic review of Zostavax data and therefore should be taken into account in this assessment.
175-176	General	Suggest adding a comment that VE for ZBPI ADL burden of interference remains stable whatever the age.	The comment that VE for ZBPI ADL burden of interference remains stable whatever age is insufficiently substantiated and will not be added to the appendix.
176	8	Please comment to Figures 1 as in the Schmader, 2012: Figure 1 shows zoster vaccine efficacy for HZ Pain and Discomfort Burden of Illness score and ZBPI ADL Burden of Interference score in all participants. In M-ITT analyses, vaccine efficacy for the ZBPI ADL Burden of Interference score diminished with age from 73% (95% CI: 47–86%) for participants aged 60 to 64 to 59% (95% CI: 11–81%) for participants aged 80 and older, but this trend was not statistically significant (p=0.52).	Due to copyright issues, this figure is excluded.
176	11	Suggest to add comments for Figure 2, as in Schmader, 2012: In participants with HZ, zoster vaccine had minimal effects on the effect of HZ on HRQL measured using the SF-12 PCS score (VE 3.9%, 95% CI: 1.1–16%) and the SF-12 MCS score (VE 5.2%, 95% CI: 9.4–18%).	Due to copyright issues, this figure is excluded.
176	22-26	Please pay attention to Gagliardi analysis (1.2.): it is focused on **severe** ADL (eg score ≥300) also reported in the primary source: Schmader, 2012 page1637. Please correct accordingly: VE for **severe** ADL interference.	The sentence is extended by the addition of VE for severe ADL interference.
APPENDIX 3			
180-181	General	Please remove the examples for each ethical, organisational, social and legal aspects, which simply copy-paste guidelines and does not refer specifically to the present REA.	Changed.

Comments of WP5 members:

Page	Line	Comments	Comments from the author:[2]
HAS (France)			
General		All remarks made by HAS have been taken into consideration. No new comments concerning the evaluation are being raised.	Thank you for your remark.
General		HAS agrees with adding trend analysis to the Result cards as they provide a clear and prompt information.	Thank you for you remark.
General		No changes concerning reimbursement status were done compared to information sent during the first reviewing process.	Thank you for confirmation.
2	1	The date of the second draft is probably not correct. If the first draft is dated 22.5.2013, the second draft cannot be dated one day before (21.5.instead of 21.6.2013).	This should have indeed been 26-06-2013 and has been corrected.
11	18	Change „was“ in „**were**“	Corrected.
22	13	Add „programme **will** involve“	Corrected.
25	44	Change „hiv-infected“ to „HIV-infected“	Corrected.
28	27	Add „in **the** youngest“	Corrected.
30	34	Spelling: „disa**d**vantage“	Corrected.
32	49	Change „was“ in „**were**“	It has been hanged to “People who have been vaccinated (…)“
32	52-53	Change „A composite endpoint has“ in „**composite endpoits have**“	It has been hanged to „Such endpoints (…)“
70	1	Delete „it ~~is~~ manifests as a“	Corrected.
74	11,14	Change to past tense.	Corrected.
94	32	Change „Europa“ in „Europe“	Corrected.
95	11	Change „undergone“ in „undergo“	Corrected.
106	44	Add the point „yet**.** France“	Corrected.

[2] After handling of the comments of WP5 members, the text has been editorial reviewed. It is possible that the suggested corrections of typographical errors are not visible anymore because the text has been rewritten.

Page	Line	Comments	Comments from the author:[2]
106	57	The situation in France is described on line 42-47 of the same page therefore please remove "HAS (France)" from the sentence.	HAS (France) will not be mentioned in this sentence.
107	11	Change „reimbursed" in „reimburse"	Corrected.
111	42	Change „variacella" to „varicella"	Corrected.
116	10	Spelling: „gp/~~v~~outpatient »	Corrected.
116	18	Speling: „i**n**ter alia"	Corrected.
134	4	Spelling: „polymyalgia~~e~~"	This has been corrected to „"polymyalgia"
140	35	Change „age 50-59 years old" in „aged 50-59"	Corrected.
141	13	Change „susceptible for" in „susceptible to"	Corrected.
156	27	Underline the title Trend analysis as it was done for other charts.	Corrected.
178	20	Add „probably **be**"	Corrected.
Organisational remarks		It would be practical to do changes to the first draft by Revisions, so that the modifications done by the author are easier to find in the text during the second reviewing process.	The second draft is intended as a consultation document for a broad panel. For the most of the stakeholders, this is a new document. In that case, track changes may cause confusion and decrease the readability. We can consider sending 2 versions to the dedicated reviewers who commented on the first draft.
Organisational remarks		Comments of reviewers could be listed by page and line of the reviewed document instead of sorting them by country.	It is a choice. Both presentations have advantages and disadvantages. In this way a member can quickly see what has been done with their comments.
KCE (Belgium)			
		Just one comment: Detailed information to investigate potential effects of dose potency and (duration of) freezing of the vaccine is not available [Bilcke 2012]. The problem is that the information (efficacy by dose potency in the RCT) is available (very briefly discussed at FDA meeting) but the company does not want to make it public in detail despite requests. This information is important as it could impact on the extrapolated duration of protection, used in models of effectiveness and cost-effectiveness [Bilcke 2012].	The point of dose-effect relation is truly relevant. In the summary of the scoping meeting we explicitly asked for information about this topic, but did not get any. Although it is an important issue, we have no reliable information to report further than we did in the report. The slides on the FDA site (backgroud information at a meeting) are not sufficient to consider it as verifiable information.

Page	Line	Comments	Comments from the author:[2]
INAMI RIZIV (Belgium)			
14	Section Outcomes	Wouldn't it more comprehensive to use here the three phases of 'zoster pain' and not 'acute pain': acute herpetic neuralgia, subacute herpetic neuralgia and post-herpetic neuralgia?	The scope (PICO) has already been set in February after the scoping meeting. In addition, there is no such information available.
16	11	Common comment with previous comment.	Please see our previous response.
17	31-33	Aciclovir, famciclovir, and valaciclovir are utilized as a antiviral treatment of herpes zoster. They reduce the severity and duration of acute pain from zoster and the risk for progression to PHN. Inaccurate: see: Li Q, Yang J, et al. Antiviral treatment for preventing postherpetic neuralgia. Cochrane Database Syst Rev. 2009 Apr 15; (2): CD006866. "There was no significant difference between the oral acyclovir and control groups on the incidence of PHN four months (risk ratio (RR), 0.75; 95% CI 0.51 to 1.11; P = 0.15) or six months (RR 1.05, 95% CI 0.87 to 1.27; P = 0.62) after the onset of the acute herpetic rash. There was some evidence for a reduction in the incidence of pain four weeks after the onset of rash. In the trial of famciclovir versus placebo, neither 500 mg and 750 mg doses of famciclovir reduced the incidence of herpetic neuralgia significantly."	The sentence in the report is meant as a general summing of applied drugs. In view of the change of the approved therapeutic indications of the antivirals, the passages hereabout will be changed and denoted as off-label use. The paragraph has been reworded as: Guidelines recommend the use of oral antiviral agents for the treatment of HZ [Dworkin 2006]. Treatment is effective if it is started within 72 hours of the onset of acute symptoms. In a few cases, the therapy is started more than 72 hours of the onset of acute symptoms because the patient delays the medical visit or because the often unusual symptoms of the disease have made diagnosis difficult for the physician. Current treatments PHN are tricyclic antidepressant drugs (TCAs), alfa-2-delta-ligands, opioids and topical agents. Aciclovir, valaciclovir, famciclovir [Schmader 1999; Sacks 2013] and brivudin have also been used to treat PHN. At the moment, antiviral drugs are not approved for PHN, only for HZ treatment.
17	45	In the publication of Opstelten 2005, only a minority of HZ patients (22,5 %) were prescribed antiviral treatment. This contrasts with the SPS Study: 85-87% of the patients were taking famciclovir.	The text has been adjusted with information of the SPS about the percentage of antiviral use.
25	24-25	In addition, subjects with a contraindication such as a compromised immune status are more likely to be harmed. Comment: As mentioned elsewhere in the report, specific studies are underway in immunodepressed patients (e.g. HIV) to study harm and efficacy of Zostavax. Until the moment these clinical data are known, compromised immune status remains a contraindication. Efficacy data on Zostavax in cohorts are already published e.g. elderly American patients with co-morbidities.	Data about real life use of Zostavax has been added and discussed in the report (D0017), including publication of Langan.

Page	Line	Comments	Comments from the author:[2]
		Article (Langan) added.	
99	3-5	These treatments reduce the duration of viral shedding and lesion formation, decrease the severity and duration of acute pain from zoster and the risk for progression to PHN [Gnann 2002; Tyring 2007] Comment. Again more accurate data are in "Li Q, Chen N, Yang J, et al. Antiviral treatment for preventing postherpetic neuralgia. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006866."	This has been reworded as follows: "These treatments reduce the duration of viral shedding and lesion formation, decrease the severity and duration of acute pain from zoster and the risk for progression to PHN [Gnann 2002; Li 2009; Tyring 2007]. According to [Li 2009], based on 12 randomised and quasi-randomised controlled trials, oral acyclovir did not reduce the incidence of PHN significantly. There is insufficient evidence to determine whether other antiviral treatments prevent PHN [Li 2009]."
172	42-43	According to the Cochrane review, the number needed to treat to benefit (NNTB) is 50 for people ≥ 60 years (SPS population). Comment: better with 95%CI.	Unfortunately, no information about confidence interval of the presented NNTB is shown in the Cochrane review. Because of inconclusive data and problems with the calculation of the NNV (NNTB) for this assessment, it is decided to omit this question for the result cards.
		Trend analysis for safety and for efficacy: fine for Zostavax but probably not always needed in future pilots. Text and graphs OK.	Agreement (The question refers only to the present assessment of Zostavax and not in general).
		Reimbursement status: OK for Belgium, namely not reimbursed.	Agreement.
GÖG (Austria)			
		do you agree to add trend analysis in the report? ***>yes***	Agreement.
		given the limitation within the REA, do you agree with our approach? ***>yes***	Agreement.
		do you have any comments about the presented data (reliability of the content)? ***>no. data presented are concise but reasonable***	Agreement.
		do you agree with the way in which we presented the data, including the places where information are put (text and graphs)? ***>yes***	Agreement.
		Check or provide (when missing) reimbursement status of the zostavax in your country. ***>reimbursement status of Zostavax in Austria as stated is correct (authorization in 2006, but***	This has been corrected.

Page	Line	Comments	Comments from the author:[2]
		currently not on market in Austria.)	
MoH Cz Rep (Czech Republic)			
		I fully agree and welcome the graphical presentation of the results by trend analysis and the graphical approach in general (either at page 133 for safety issue or 153, 157, for the outcomes efficacy)	Agreement.
CAHIAQ (Spain)			
1	1	One of the dates in this table should be corrected.	Corrected.
3	19	before THE reviewing process?	Corrected.
6	9	I am not a native English speaker but this expression (to experience zoster) sounds a bit strange to me.	This has been checked by medical editor who is native speaker.
6	9	HZ instead of zoster?	Corrected.
6	9	Should it be Varicella Zoster virus (capital letters)? If not, maybe Herpes Zoster at the beginning of the paragraph should be reviewed.	This has been checked by medical editor.
6	12	Delete fullstop.	Corrected.
6	13	HZ	Text has been modified.
6	30	Delete fullstop. This is valid throughout the text.	Additional fullstops have been removed.
7	1	tend instead of tread	This has been changed to “suggest”
7	4	Because this is a brand name, should it not include de symbol for registered brand? This applies throughout the document.	MAH as well as medical reviewer did not have similar comment on that issue. No change has been provided.
7	7	HZ. Correction applies to all the text.	Corrected.
7	7	Delete "a"	Corrected.
7	14	delete "the"?	Corrected.
7	21	Delete "the"?	This has been consulted with medical editor. No change is needed.
7	22	guidelineS in plural?	Corrected.
7	22	Suggestion: identifies systemic antiviral therapy as first line	Corrected.

Page	Line	Comments	Comments from the author:[2]
		choice.	
7	34	Shouldn't the indication be mentioned first?	Added a sentence: Zostavax is indicated for prevention of HZ and HZ-related PHN. It is indicated for immunisation of people aged 50 years or older."
7	34	change format.	Format has been changed..
7	51	One	It is "ones", different potencies and formulation have been studied in clinical trials.
8	10	that included /including	This has been substituted with enrolled.
8	12	including	Sentence has been changed according to the suggestion of the medical reviewer.
8	16	Median? Does this median follow-up apply to both the primary study and the substudy?	This refers to the ZEST and not to the SPC. The ZEST has no substudy and the mean follow-up of the ZEST was 1.3 years.
8	17-18	Is VE ever used again?	Based on the comments of the medical editor we try not to use the abbreviation but use vaccine efficacy instead.
8	28	Zostavax?	Zostavax is the only zoster vaccine now available. Therefore these terms are synonyms.
8	34	One always learns something! Nice word!	Vaccinee (person who was vaccinated) is not an uncommon word in that field.
8	38	People >50 are all considered elderly? I would expect this term to be used in older people.	Word "elderly" has been eliminated.
8	40	benefit	Typo has been corrected.
8	40-42	maybe the sentence could be shortened.	The length of the sentence has been consulted with medical editor.
8	44	has not been demonstrated? If can not is mantained in the sentence, it should be changed for cannot.	The sentence has been changed.
8	46-48	has not been demonstrated? If can not is mantained in the sentence, it should be changed for cannot.	The sentence has been corrected.

Page	Line	Comments	Comments from the author:[2]
9	5	Throughout diffent countries in Europe	It has been changed to “within Europe”
10	1, table, column 1	I think the use of the slash is a bit confusing and I do not think this column adds important information.	Indeed, the summary table contains lots of information about benefit and harms of Zostavax and can be confusing. On the other hand, it is showing in a snapshot the most important outcomes for the several age groups. We have payed attention to a better lay-out of the table and among other changes the first colum has been removed as well.
10	5	*BOI in 50-59 is calculated over a 21-day period following HZ rash onset. BOI in ≥60 yrs, is calculated over a 182 day-period.*	Yes. This information could be found in the note (∫) under the table.
11	4	differences	The word “difference” has been kept after consultation of medical editor.
11	4	why is the comparative form used here?	The comparative form was used to show the difference between sample sizes between study on HZ prevention and PHN prevention.
11	11	shows	This has been corrected to “showed”.
11	16	If it is contraindicated there is no need for this information even if this is very relevant from a clinical point of view	There is also a need for information about the contraindicated group. This is a group who need a vaccination probably the most, and in the practice they will be vaccinated too.
11	18	This sentence should be rewriten.	The sentence has been rewritten.
11	21	both	This has been clarified.
11	21-24	Composite endpoints can be difficult to interpret and their misinterpretation mey result....	The sentence has been rewritten.
11	26	Methods for pain assessment?	This has been corrected.
11	33	Long term or long-term	This has been corrected to “long-term”.
11	45	compared	This has been changed to “compared with”.
11	47	predefined?	This has been corrected.
11	49	delete "a"	“a” has been deleted.
14	Intervention	®: This is the symbol I referred to previously.	Thank you for clarification.

Page	Line	Comments	Comments from the author:[2]
14	Comparison, 1)	Delete "the"	It was decided to keep this article.
14	Comparison, 2)	At present?	It has been decided to keep “at this moment”
14	Comparison, 2)	Available drugs are ...	The sentence has been rewritten.
14	Comparison, 2)	include:	The sentence has been rewritten.
14	Comparison, 2)	cream?	The sentence has been rewritten.
15	25	HZ! Homogenization is requiered throughout the text	This has been corrected.
16	12	this acronym has already been presented	This has been corrected.
16	31	don't understand the use of "also".	It has been changed to ”always”
16	34	It IS highly dependent	This has been corrected.
16	41	make IT difficult?	This has been corrected.
16	43	Not sure about the use of this connector.	The sentence has been reformulated.
17	1	tend	This has been corrected.
17	2-4	this sentence needs to be reviewed	Sentence has been corrected.
17	5-6	Despite several studies to assess health care have been conducted in different European countries, resource use caused by HZ and PHN management,	This has been reformulated as follows: “In European countries several studies have been conducted to assess health care resource use as a result of HZ and PHN management. The methodologies of these studies differ so direct comparisons are not possible.”
17	7	have been?	No change was needed in this case.
17	14	patients	This has been corrected.
17	17	are?	This has been corrected
17	22	review the use of capital letters. seen in differnt places	This has been corrected.
17	29	delete "the"?	The sentence has been rewritten.
17	40	comments in the summary apply	This has been corrected

Page	Line	Comments	Comments from the author:[2]
17	44	this reference should be reubicated	It is not clear what kind of change was suggested here.
18	5	delete "the"?	This has been corrected.
18	11	is this "another study relevant". When referred as "another" it does not seem to be relevant.	The other study (Schmader 2012) is referring to the ZEST. This name has been added.
18	26	comments in the summary apply	The sentence has been rewritten.
18	27	options	This has been corrected.
18	32	the exclusion of zostavax from the reimbursement scheme?	An option is not to reimburse at all. Text is changed to: no reimbursement for Zostavax.
18	36	text below dos not seem to be "results"	This is the result of the first domain about health problem and current use of the technology. For details please see model for rapid REA and the template for doing assessment.
21	1	reference should be reubicated	It is not clear what kind of change was suggested here.
21	6-7	this sentence should be reviewed	The sentence has been rewritten.
21	17	the	This has been corrected.
21	39	Is this relevant at this point?	Yes, the comparator is important. For details please see model for rapid REA and the template for doing assessment.
22	12	the first-ever national shingles immunisation campaign in Europe is expected to be launched [soon] in the UK	The sentence has been rewritten.
22	14	involves/will include	This has been corrected.
23	28	are?	This has been corrected.
24	9	I think, reference to this study is diffents in previous pages. I think it was written Zest	As stated in the text: the first two percentages refer to the SPS substudy and the last two percentages to the ZEST.
24	21	is?	This has been corrected.
24	26	latter case of substudy? I do not understand the meaning.	The overall study of the SPS contained almost 40000 subjects, a part of them are studied further in the substudy. The following info is referring tot the population of the substudy and not to the total population of the SPS. The sentence has been rewritten for better understanding.

Page	Line	Comments	Comments from the author:[2]
24	38	AE. this comments applies to all the text. Check the use of the abbreviation.	This has been corrected.
24	39	higher?	Twice the change to get a side effect is indeed higher risk.
24	39	have/experience instead of get?	Sentence was correct, however it has been changed for better readability.
24	44	of?	This has been corrected.
24	52	in different age groups?	Sentence has been changed to: “Age-related information is not available”.
25	1	up to 10 years after vaccination?	This has been changed to “until 10 years after vaccination (…)”
25	3	MAH?	Yes. Text is changed to MAH.
25	4	besideS	This has been changed to “in addition to”.
25	10	differences	This has been corrected.
25	12	SAE	This has been corrected.
25	19	increasing age? in older population?	Text is changed to ’increasing age’.
25	21	just to confirm: 219%?	Yes, this is twice the chance as compared to the control group.
25	28	depending on the country?	Indeed, it remains a choice of the country. This has been reformulated for better readability.
25	44	HIV	This has been corrected.
25	46; 50	AE	This has been corrected.
26	1	EXPERIENCE?	This has been changed to “of having”
26	3	(S)?	AE including SAE were studied using the frozen formulation and not the current refrigerated formulation. Presentation of the abbreviation “(S)AE” seems to be correct.
26	8	vaccine self? Maybe vaccine ITself?	This has been corrected according to the suggestion of the medical reviewer.
26	13	HIV	An example of HIV-infected adults has been removed.

Page	Line	Comments	Comments from the author:[2]
28	19	reference to people of a certain age used the symbol ≥. Homogenizations is requiered throughout the text.	The text has been checked and corrected in order to make it more homogenous.
28	27	in THE youngest ages group?	This has been corrected.
28	31	placebo group.	This has been corrected.
28	41	is A potenctial...	This has been corrected.
28	42	the	This has been corrected.
29	12	the efficacy of the vaccine in ...	This has been changed to “the efficacy of Zostavax (…)”
29	15	HZ	This has been corrected.
29	20	this abbreviation has not been used before	The abbreviation of yo has been removed and replaced by the full term (years old) in place.
29	23-27	this sentence should be reviewed	The sentence has been reviewed.
29	28	I do not think GOOD should be the terM to be used.	This has been changed to “clear relationship”
29	31	Tthis term should be reviewed	This is not clear which term is meant here.
29	35	previous comment applies.	This is not clear which term was meant in the previous comment.
29	36; 38	PHN	This has been corrected.
29	41	compared	This has been corrected.
29	47	this expression should be reviewed	Sentence has been reviewed and corrected.
29	52	concluded/concludes	This has been corrected.
29	52	is effective?	This has been corrected.
29	54	In other words, there is no evidence that zoster vaccination is effective in reducing PHN in subjects with a higher burden.	This sentence has been removed from the paragraph.
30	1	According to Oxman	This has been corrected.
30	2	reduces pain in 3 days?	This has been changed to
30	3	this expression should be reviewed	This has been reviewed and changed.
30	3	i would avoid the use of specific	It is about specific data. General data about pain, incorporated in a

Page	Line	Comments	Comments from the author:[2]
			composite outcome have been presented.
30	9	I think this is previously described in the first pages	An age dependent effect of Zostavax has indeed been mentioned before. This sentences is specifically referred to the outcome of BOI.
30	10	this expression shopuld be reviewed	The sentence has been rewritten.
30	12	i would not qualify the relation as good or bad.	This has been changed to “clear relationship”
30	18	the	This has been corrected.
30	42	has	This has been corrected.
30	49	the use of shown means to be something has been demosntraed. Is that the case or is it that data seem to show efficacy is mantained for up to 7 years?	This has been replaced with “persists”. Data for 10 years were collected but not yet published.
30	53	this term has been used before	This has been corrected.
31	1	described?	The sentence has been rewritten.
31	19	This expression should be reviewed.	Expression has been reviewed and sentence rewritten.
31	29	These risks make the elderly people an interesting target population for zoster vaccine as they have the highest burden.	The sentence has been rewritten as follows: “As a result, elderly people are most affected by HZ and are the most appropriate target population for HZ vaccine”.
31	47	Zostavax reduced...	Suggested change has not been considered necessary.
32	42	shows	This has been changed to “showed”
32	49	are/were	This has been changed to “have been”
32	52	a previous comment applies also to this sentence	The sentence has been reviewed.
33	3	a previous comment applies also to this sentence	The sentence has been reviewed.
33	4	Besides	This has been corrected.
HVB (Austria)			
7	22	Which Austrian document refers to German guidelines? Please let me know so we can check	The following was reported in the MAH’s submission file: “Austrian dermatologists do officially refer to the guidelines of the German Dermatological Society.

Page	Line	Comments	Comments from the author:[2]
			For the situation in Germany, the MAH referred to two guidelines. - German Dermatology Society - Herpes zoster guidelines; Gross et al. J Clin Virol 2006 (HZ and PHN). -German Society of Neurological Pain - Leitlinie Neuropathischer Schmerz _Deutsche Gesellschaft für Neurologie Guidelines for neuropathic pain; Leitlinien der DGN 2008 (neuropathic pain). PS. On the website of the Austrian society of dermatology and venerology (http://www.oegdv.at/cms/.) no hits can be found for the search terms: herpes zoster, postzosterschmerz or (neuropathischen) Schmerzen.
8	1	This statement does not belong here, should be under results, line 8	The statement is considered as a description of the current clinical practice and not as a result of trials. Therefore, we prefer to keep this sentence in the current place.
9 18	8-9 33-34 Table	Austrian vaccination plan recommends vaccination with zoster vaccine, but this is contingent on the availability of the vaccine. Since it is not available in Austria, there is no recommendation. Consider including availability in table http://bmg.gv.at/cms/home/attachments/3/3/6/CH1100/CMS1327680589121/impfplan2013.pdf See also comment by BIQG/GÖG	Information about the reimbursement state and availability of Zostavax is put in A0021. The table has been deleted.
11 21	10-14 5	Is there a reason to assume different effects on outcomes if antibody generation does not differ between the two formulations? EMA did not consider this an issue when approving the new formulation. Please elaborate.	In designing bridging studies, it is important to consider the critical immunological parameters for determining comparability of immune responses. EMA guidelines on Clinical Evaluation of New Vaccines requested comparative immunogenicity studies in case of formulation changes. In the study of Gilderman et al, the VZV antibody geometric mean titer (day 28), the VZV antibody geometric mean rise (day 1 versus day 28) been chosen as primary endpoints. In this study, it was indicated by the authors, that endpoints correlated best with protection to HZ. This was criticized by M.J. Levin et al. [Levin 2009], who indicated that there is no direct evidence that these endpoints are the ‘ best correlation’ for immunity postvaccination. In elderly patients with HZ the severity of the HZ correlates with the magnitude and tempo of VZV-specific T-cells (early effector and effector memory populations) appearance, but not with the magnitude of VZV-

Page	Line	Comments	Comments from the author:[2]
			specific antibody. Levin indicated that the paper of Gilderman provided no data on the relationship of GMR to HZ. In the sight of these discussions, we feel it is essential to mention these doubts upon the meaning of this bridging study and stated our questions whether the Gilderman study has actually shown that both formulations of Zostavax have the same vaccine efficacy. The reference to the EMA guideline has been added to the text.
20	B0003 B0008 B0009	These are not phrased as questions.	This has been changed.
AIFA (Italy)			
		General comment: For this first pilot of JA2 it would have been worthwhile to test the HTA Core model for REA of pharmaceuticals by assessing a medicine having an active comparator. It would have helped to apply and test methodologies and tools developed so far in REA.	Thank you for your comment. Medicine having active comparators will be tested already during the second pilot.
6	Table	Change „QUALITY OF LIFE“ with „HEALTH RELATED QUALITY OF LIFE“.	This has been changed.
7	21	In Italy according to the Note 84 (Notes are regulatory tools which define reimbursed treatments for a specific condition to guide physicians to prescribe the most appropriate treatments) aciclovir, famciclovir, valaciclovir, brivudin are covered by NHS for the treatment of VZV. • aciclovir 800 mg x 5 / die; • valaciclovir 1000 mg x 3 / die; • famciclovir 250 - 500 mg x 3 / die; • brivudin 125 mg x 1 / die. Pregabalin and gabapentin are reimbursed for the post-herpetic neuralgia caused by HZ (Note 4).	Dosage information can be found in A0025.
7	32	It would be appropriate to report the European therapeutic indication granted for the product.	European therapeutic indication has been reported.

Page	Line	Comments	Comments from the author:[2]
8	17	The secondary endpoints could be reported as well.	Information about the secondary endpoints are added in the text.
8	28	Minor change: events.	Typo has been corrected.
9	Table	The information about the coverage in Italy could be added in table. (Not reimbursed) since it is reported in result card A0021 of the report.	This table has been deleted.
11	10-14	It is suggested deleting the phrase since it relates to a benefit risk assessment which has been already evaluated in November 2006 (Variation EMEA/H/C/000674/II/0002) by the CHMP as variation to the initial marketing authorisation of May 2006..	CHMP granted the market authorization on an intermediate outcome (antibody titer). The issue addressed here is about the uncertainties upon the effectiveness of the vaccine.
14	Last line of table	Change „QUALITY OF LIFE“ in „HEALTH RELATED QUALITY OF LIFE“.	The term has been changed.
15	21	In this paragraph only methods applied for producing synthesis should be described as in the other domains.	Text has been revised.
17	14	Minor change: Higher hospitalisation rate is reported for female patients.	Typo has been corrected.
17	40	Change “offical” with “official”.	Typo has been corrected.
17	40	In Italy according to the Note 84 (Notes are regulatory tools which define reimbursed treatments for a specific condition to guide physicians to prescribe the most appropriate treatments) aciclovir, famciclovir, valaciclovir, brivudin are covered by NHS for the treatment of VZV. • aciclovir 800 mg x 5 / die; • valaciclovir 1000 mg x 3 / die; • famciclovir 250 - 500 mg x 3 / die; • brivudin 125 mg x 1 / die. Pregabalin and gabapentin are reimbursed for the post-herpetic neuralgia caused by HZ (Note 4)	The following sentence has been added: “In some other countries (i.e. Italy), HZ treatments that will be reimbursed, are identified by the regulatory agency.”
17	39-40	Suggestion of rewording the phrase since the absence of recent guidelines is reported in the majority of countries and not only in	The phrase has been rewarded as follows: Substantial differences in HZ management exist in the different European countries. Many

Page	Line	Comments	Comments from the author:[2]
		Italy and France "A lack of recent official guidelines for HZ exists in the majority of countries".	countries lack recent official guidelines for HZ. In some other countries (i.e. Italy), HZ treatments that will be reimbursed, are identified by the regulatory agency.
18	4	Suggestion of deleting the phrase since the population aged 50-59 has been studied in the Protocol 010 and Protocol 011 (both randomised, controlled double blind multicenter studies). Protocol 010 and 011 were the clinical trials submitted by the manufacturer for the variation intended to expand the indication of ZOSTAVAX to individuals ≥ 50 years of age for the prevention of HZ and its complications. Variation EMEA/H/C/000674/II/0002 was adopted by the CHMP in November 2006.	Unfortunately, it is not clear what the reviewer means by this point. This section is meant to name both formulations of Zostavax (frozen and refrigerated).
18	16	It seems a repetition of what reported in page 17 line 22-26.	The repetition has been removed.
19	46	Country specific decisions on Zostavax reimbursement and use: This point should be better explained, as it's not clear what it is the point of discussion	This bullet point has been removed as the country specific reimbursement status is a fact and not appoint for discussion.
21	38	Suggestion of correcting the phrase "ZOSTAVAX should not be administered to pregnant women; furthermore, pregnancy should be avoided for **ONE month** following vaccination [EMA 2013; CDCP 2008]". The product information has been amended to reflect that pregnancy should be avoided for 1 month following vaccination instead of 3 months as in the first authorisation. (EPAR 13 February 2013, EMA/78658/2013).	The sentence has been corrected.
25	14	Change "age" in "aged".	Typo has been corrected.
25	18	It seems a repetition of what reported in page 24 line 37-43.	Both lines are dealing with the increased risk for a SAE by age. The paragraph has been removed.
25	24-25	The phrase "In addition, subjects with a contraindication such as a compromised immune status are more likely to be harmed" seems to be redundant, since the vaccine is contraindicated in immune compromised subjects because of safety reasons.	True, it seems obvious. The background of this sentence is the reflection on the daily practice. Patients with a contraindication will need a vaccination the most, and in the practice they probably will be vaccinated too. See also results card D0017 for real life data of patients with a contraindication.
26	13	See comment at page 24- line 24-25.	See above (it is page 25 line 24-25 of the draft version)

Page	Line	Comments	Comments from the author:[2]
63	table	Off label and immunocompromised (Table).	The word immunodepressed is change into immunocompromised.
64	16	VZV instead of VSV	Typo has been corrected.
64	31	VZV instead of VHZ	Typo has been corrected.
90	25-27	Suggestion of deleting the phrase "The studied population differs from the one detailed approved by regulatory authorities. In the Shingles Prevention Study [Oxman 2005] eligible were adults 60 years of age or 27 older with an history of varicella." since the population aged 50-59 has been studied in the Protocols 010 and 011, whose results have been also reported in the Efficacy domain of this report.	The text has been changed to 'The studied population is not exactly the same as the population approved by regulatory authorities, more groups of patient have been excluded from the trial.'
90	41	Delete „$"	This has been corrected.
91	7-9	Minor change: „In clinical studies vaccine efficacy **was investigated** in people adults 60 years of age or 8 older and aged 50–59 years. Immunocompromised persons were excluded both in the Shingles Prevention Study [Oxman 2005] and in the **ZEST** study [Schmader 2012].	This has been corrected.
94	32-33	Minor change: There are no **published** data from **EUROPE** regarding the utilisation of this technology because this technology is not used yet in most European countries.	This has been corrected.
95	6	"among those with immune suppression (2.3% vs. 2.1%)." This population is not contraindicated in USA?	Imunosuppression or immunodeficiency are indeed a contraindication in the USA. However in the cohort study of Langan 2013, immunosuppression status is considered at any stage during the study (retrospective), not only at the moment of vaccination.
95	11-12	"and immunosuppressed people were more likely to undergone vaccination". See previous comment.	Although a low number of persons with a immune suppression, the percentage of people who has got a vaccination (2,3%) is slightly higher than those without a notification of immune suppression at any state during the study (2,1%).
97-98	41-44 1-2	This phrase relates to diagnosis, can it be moved in the previous result card **[A0024]** ?	Paragraph has been moved to A0024 (with related reference).
98	11	Suggestion of rewording *"In many cases, such as in Italy, patients seek medical advice at a late stage (please add the reference). A*	The paragraph has been reworded.

Page	Line	Comments	Comments from the author:[2]
		lack of recent official guidelines for HZ exists in the majority of EU countries (e.g in France the last one refers to 199). For Italy see comment page 17 line 40.	
118	50	Change "monitoringsystems" in "monitoring systems".	Typo has been corrected.
113	13	Authors say that limited access to Zostavax was reported in different countries (Austria, Denmark etc..) due to the complex manufacturing process. Further motivations should be provided about the complexity of manufacturing process because it impacts on product availability and denying, consequently, patient access to vaccine.	Motivating difficulties in the production process is out of the scope of this rapid REA.
113	16	It could be also add the Italian provision of Zostavax: "In Italy this product is not reimbursed by the National Health Service. It can be bought by the patient with the medical prescription but the product is not marketed in Italy".	Information about the reimbursement state of Zostavax is put under A0021.
120	33-34	The authors say that "The monitoring and presence of a specific register could be overlapping with the traditional pharmacovigilance systems implemented at national level." We do not totally agree with this statement because the two registries could integrate some missing information.	The sentence has been reworded as follows: "The monitoring and presence of a specific register could be **partially** overlapping with the traditional pharmacovigilance systems implemented at national level."
122	20	Minor change: based.	Typo has been corrected.
147	20-22	Change "age" in "aged".	Typo has been corrected.
178	20	Delete "The truth will probably somewhere in between" since too informal.	This sentence is deleted
178	21	Change "seem" in "seems".	Typo has been corrected.