

VACCINATION AGAINST HERPES ZOSTER

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ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL no. 9684

Vaccination against Herpes Zoster

In this scientific advisory report, which offers guidance to public health policy-makers, the Superior Health Council of Belgium provides recommendations on the prevention of herpes zoster infections in the Belgian population.

This report aims at providing public authorities with specific recommendations on vaccination against Herpes Zoster (Shingles).

This version was validated by the Board on the 3rd of August 2022.¹

I INTRODUCTION

The varicella zoster virus (VZV) is responsible for two distinct clinical syndromes.

Primary VZV-infection induces varicella (chickenpox), an infectious skin disease that typically affects children. There are several (monovalent and combined) vaccine formulations against primary VZV-infection available on the Belgian market. For the guidelines on preventing primary VZV-infections in children, we refer to advisory report No. 9212 of the Superior Health Council (SHC).

VZV can reactivate after several decades and cause herpes zoster (HZ, shingles). This localised or generalised, painful skin eruption mainly affects older adults. Around one third of the population will experience HZ in the course of their lives. Postherpetic neuralgia (PHN) is a complication of HZ that can cause chronic pain for several months or even years also with increasing incidence in the older population.

In Belgium, a live attenuated vaccine Zostavax® (MSD) and a non-live adjuvanted recombinant subunit vaccine against HZ, Shingrix® (GSK) are registered.

This report sets out the recommendations vaccination against HZ and PHN and is an update of the previous report SHC 9209.

¹ The Council reserves the right to make minor typographical amendments to this document at any time. On the other hand, amendments that alter its content are automatically included in an erratum. In this case, a new version of the advisory report is issued.

II CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Findings from clinical and post-marketing studies on the adjuvanted recombinant subunit vaccine against HZ (Shingrix) indicate that:

- ZOE-50 study (NEJM 2015) with a VE of 96 % after a 4 year period. Results were confirmed among old persons aged over 70 years, (ZOE-70 study), even in an old frail population.
- Robust immunologic responses were found in immunocompromised patients along with an acceptable safety profile.
- Recombinant HZ subunit vaccine reduces also the risk of PHN (VE of 89-91%).
- Results were confirmed in real-world studies showing VE between 70-86 %.
- Results of VE are higher for recombinant HZ subunit vaccines compared to livedattenuated HZ vaccine.
- Intermediate results of long-term follow-up studies are showing that VE remains high (over 90 %) after 7 years of follow-up.
- Vaccination against HZ is safe. Injection site reactions and mild to moderate systemic reactions were the most reported side effects. Serious adverse events were similar between the vaccination and the control group.

Recommendation:

The SHC recommends vaccination against Herpes Zoster with a non-live adjuvanted recombinant HZ subunit vaccine (2 dose regimen) for:

- Immunocompetent adults aged \geq 60 years.
- Immunocompromised patients, including those under immunosuppressive therapy aged ≥ 16 years and also patients under treatment with anti-JAK therapy (<u>SHC 9158 chapter 5</u>).

Co-administration with the seasonal influenza vaccine or pneumococcal vaccine (PPV23 or PCV13) or dTpa is safe.

The SHC is aware of the high cost of the vaccine at this moment and suggests to take into account cost-effectiveness studies and the results of the ongoing Health Technology Assessment of the Shingrix vaccine by KCE (results expected later this year).

Keywords and MeSH descriptor terms²

MeSH terms*	Keywords	Sleutelwoorden	Mots clés	Schlüsselwörter
Vaccine	Vaccine	Vaccin	Vaccin	Impfstoff
Adults	Adults	Volwassenen	Adultes	Erwachsene
Herpes zoster	Herpes zoster	Herpes zoster	Herpes zoster	Herpes Zoster
Postherpetic	Postherpetic	Postherpetische	Névralgie post-	Postherpetische
neuralgia	neuralgia	neuralgie	herpétique	Neuralgie

MeSH (Medical Subject Headings) is the NLM (National Library of Medicine) controlled vocabulary thesaurus used for indexing articles for PubMed <u>http://www.ncbi.nlm.nih.gov/mesh</u>.

² The Council wishes to clarify that the MeSH terms and keywords are used for referencing purposes as well as to provide an easy definition of the scope of the advisory report. For more information, see the section entitled "methodology".

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IV METHODOLOGY

The Board and the Chair of the area Vaccination identified the necessary fields of expertise. An ad hoc working group was then set up which included experts in infectiology, geriatrics, epidemiology, rheumatology, general medicine, pharmacovigiliance and vaccinology. The experts of this working group provided a general and an ad hoc declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.

This advisory report is based on a review of the scientific literature published in both scientific journals and reports from national and international organisations competent in this field (peer-reviewed), as well as on the opinion of the experts.

KCE performed a systematic literature research on Shingrix in the frame of an on-going Health Technology Assessment of Shingrix vaccine (publication in October 2022), the synthesis of their research was used to update the report.

A hearing was organised for GSK on 9 February 2022 on Shingrix for the ad hoc working group.

Once the advisory report was endorsed by the NITAG by mail on July 18 2022 it was ultimately validated by the Board.

V ELABORATION AND ARGUMENTATION

List of abbreviations used

AIDS BOI	Acquired ImmunoDeficiency Syndrome Burden Of Illness
CNS	Central nervous system
CMI	Cell Mediated Immunity
COPD	Chronic Obstructive Pulmonary Disease
DIC	Disseminated Intravascular Coagulation
gpELISA	Glycoprotein Enzyme-Linked ImmunoSorbent Assay
HAS	Haute Autorité de Santé
HIV	Human Immunodeficiency Virus
HZ	Herpes Zoster
INFY ELISPOT	INterFeron γ Enzyme-Linked Immunospot
NSAID	Non-Steroidal Anti-Inflammatory Drug
PCR	Polymerase Chain Reaction
PHN	Postherpetic Neuralgia
QALY	Quality-Adjusted Life Year
RA	Rheumatoid Arthritis
RCF	Responder Cell Frequency
SHC	Superior Health Council
VZV	Varicella Zoster Virus
VE	Vaccine efficacy

1 Herpes Zoster

1.1 The infection

Most of the adult population (95 %) has been infected with the VZV (Kogore et al., 2003). In the course of primary infection, the skin rash that is typical of varicella develops after the viraemic phase. The VZV then migrates retrogradely via the sensory nerve endings to the nerve bodies of the dorsal root ganglia, where it persists in a latent state (1 to 7 % of the sensory dorsal root ganglia contain latent VZV with < 10 genomic copies/cell) (Arvin, 1996; Wang et al., 2005). Yet it may reactivate to form intact virions that travel to the nerve endings and spread in the skin. HZ typically causes pain, followed by a vesicular rash along the dermatome of the affected sensory nerve (Arvin, 2005). Whilst there remains some uncertainty regarding the precise factors involved in reactivation, cell-mediated immunity (CMI) appears to play an important protective role. CMI against the VZV is hypothesised to be maintained through periodic subclinical endogenous reactivation and boosting due to exposure to someone with an exogenous primary VZV-infection (Hayward et al., 1991; Thomas et al., 2002).

Although there is only 1 VZV serotype, there are multiple genotypes that display geographic segregation as well as recombination (Oxman et al., 2010).

1.2 Clinical characteristics of HZ and PHN

HZ-episodes vary in severity, with less severe infections found in children and young adults.

HZ typically begins with a *prodromal* phase that may precede the HZ-skin rash by several days or weeks. The symptoms may include headache, photophobia, malaise, and less frequently fever. Abnormal sensations and pain of varying intensity in the skin are frequent occurrences. The pain may have a dull, burning or stinging quality. Prodromal pain is uncommon in persons under 30 years of age but it occurs in the majority of patients with HZ over the age of 60 years. Hypersensitivity to touch, pain caused by minor stimuli and intense itching are often described (Gilden et al., 1991). The infection is rarely confined to these symptoms without an evident HZ-skin rash (*zoster sine herpete*) (Gilden et al., 1992).

HZ will typically manifest as a unilateral skin rash that does not cross the body's midline, and will be limited to 1 or 2 (most commonly thoracic, cervical or ophthalmic) dermatomes. The rash evolves from a maculopapular erythema to clusters of clear, confluent vesicles that subsequently turn into pustules, ulcerate and then form scabs. The HZ-rash lasts between 7 and 10 days, with full recovery after 2 to 4 weeks (Rogers et al., 1971). Skin bacterial superinfection of the HZ-rash may occur (Gnann et al., 2002).

PHN, which is caused by HZ-induced neuronal damage, is a common complication of HZ. PHN is defined in terms of the duration as pain persisting \geq 30 days after the appearance of the

HZ-rash. PHN neuralgia can cause pain of varying intensity that lasts from several weeks to several years. Half of the patients describe debilitating pain that occurs on an almost daily basis and may persist for a few minutes but may also be constant. PHN can significantly affect physical and psychosocial well-being (Katz et al., 2004). Risk factors for HZ progressing to PHN are age, the severity of the pain before and during HZ, the extent of the HZ-rash, trigeminal and ophthalmic nerve lesions and viraemia (Jung et al., 2004).

In 10 % to 15 % of the cases HZ may also manifest as HZ ophthalmicus (keratitis (with corneal ulcer), conjunctivitis, uveitis, (epi)scleritis, retinitis, choroiditis, optic neuritis, ptosis, eyelid retraction, glaucoma) (Shaikh et al., 2002). Lesions on the tip and side of the nose indicate involvement of the nasocilliary bronc which also innervates the eye. If the nose is affected, extra attention should be paid to the eye. Less frequent manifestations of HZ are Ramsay Hunt syndrome (peripheral facial palsy and HZ in the external ear, tympanic membrane with our without tinnitus, vertigo or deafness), Bell's palsy ("idiopathic" facial paresis), non-cranial nerve zoster-paresis, focal neurological deficits (granulomatous angiitis), myelitis, aseptic

meningitis, meningoencephalitis and Guillain-Barré syndrome (Sweeney et al., 2001; Adour, 2001; Braverman et al., 1997; Thomas et al., 1972).

In individuals with impaired immunity, HZ can be more severe and of longer duration (Gann et al., 1991). Complications include necrosis of the skin and scarring. Disseminated HZ only occurs in immunocompromised individuals. Between 10 and 50 % of the cases of disseminated HZ involve visceral dissemination through viraemia, resulting in pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy. Visceral dissemination is associated with a mortality rate of 5-15 % (Merselis et al., 1964). In HIV-patients, visceral dissemination is less frequent, but HZ can cause a more atypical skin rash (Glesby et al., 1995).

The diagnosis of HZ is usually made on a clinical basis in the event of a typical manifestation (Opstelten te al., 2007). HZ needs to be distinguished from other skin conditions (herpes simplex, impetigo, folliculitis,). Tzanck smears, virus isolation in vesicle fluid, antigen detection, PCR and serology can be used to underpin the diagnosis (Gnann et al., 2002).

1.3 Risk factors for HZ

1.3.1 Age

Age is a strong risk factor for the incidence of HZ and PHN. In a WHO report published in 2014, the incidence of HZ was doubled when comparing people under 40 years old and over 60 years (2-4 and 6-10 per 1000 person-years respectively) in different selected countries. In Belgium, the rate of general practitioner consultations was 3 fold increased when comparing under 40 years and over 60 years people (4 and 12 GP consultation per 1 000 person years respectively (see graph below). A decrease in cellular-mediated immunity with ageing, a high number of comorbidities, a polypharmacy and a high rate of disabilities are all potential contributors to this increased risk. Age-related changes of the immune-system include a decrease of bactericidal activity and phagocytic capacity, a decrease of the number of naïve T-cells, a lower CD4/CD8 ratio, an increase of the number of memory and effector cells, a higher rate of autoreactive antibodies and a release of pro-inflammatory cytokines (IL-6 and IL-10 for example).

Figure: The influence of age on HZ consultation and hospitalization rates (Belgium) (Bilcke et al., 2012)



Fig. 2. Annual age-specific number of herpes zoster (HZ) patients with at least one general practitioner (GP) consultation per 100^{-0} (Scientific Institute of Public Health data, 2006–2008). As the observed rates for ages 102 and 103 are very high (8402 and 15248/100000, respectively), these points are not presented in this plot because it would make the plot less informative. Only patients for whom information on age and/or gender was available, are included (97.8%).



Fig. Average annual number of hospital admissions/100 000 population for primary-cause herpes zoster (HZ), by age (Minimal Clinical Data database, 2000–2007).

1.3.2 Gender

In some studies, women appear to be at a greater risk of contracting HZ (+ 11-38 %) and PHN than men (Oxman et al., 2005; Opstelten et al., 2006). However, this could not be confirmed by other studies (Donahue et al., 1995).

1.3.3 Race

Black individuals appear to develop HZ less frequently (54-75 %) than white individuals (Thomas et al., 2004).

1.3.4 Immunity

CMI-deficiency is a major determinant of the risk of contracting HZ. This accounts for the fact that individuals with advanced age, haematological malignancies (e.g., Hodgkin's lymphoma, solid tissue tumours, bone marrow transplantation, organ transplantation, and HIV) display an increased risk of HZ. An increased incidence has also been documented in the event of inflammatory diseases (systemic lupus, rheumatoid arthritis, Wegener's granulomatosis, Crohn's disease and ulcerative colitis, and multiple sclerosis).

1.3.5 Exposure to VZV

HZ does not induce varicella-epidemics. Exposure to varicella can reduce the risk of HZ through exogenous boosting of VZV-immunity (Thomas et al., 2002). It is difficult to assess the extent of the effect of Varicella exposure on the epidemiology of HZ in the elderly as well as its duration.

1.3.6 Other risk factors

Surgery, trauma and genetic factors may predispose to HZ (Thomas et al., 2004; Haanpaa et al., 2002). The role of stress as a risk factor for HZ is not clear (Schmader et al., 1990). Micronutrients could have a protective effect against HZ. Malignancy up to five years pre HZ, depression up to one year pre or post HZ, fractures up to two years pre HZ, asthma, autoimmune diseases, and immunosuppressive medication one year pre or post HZ were also associated with HZ (Ogunjimi et al., 2015).

1.3.7 Risk factors of PHN

In a recent meta-analysis, independent risk factors for PHN were Age [OR =1.59; 95 % CI: (1.23, 2.04)], acute severe pain in the herpes stage [OR =1.49; 95 % CI: (1.08, 2.08)], prodromal symptoms [OR =2.00; 95 % CI: (1.16, 3.44)], and severe rash [OR =2.40; 95 % CI: (1.83, 3.14)] (Zhou et al., 2021).

1.4 Epidemiology

1.4.1 Belgian Network of Sentinel General Practices (Sciensano)

The Belgian network of Sentinel General Practices (SGP) registered HZ cases from year 2006 to 2012 and resume registration in 2021. In 2012, this network included 146 SGPs (for 172 GPs) covering around 175 000 citizens (1.6 % of the Belgian population; 1.8 % of the Flemish region, 1.1 % of the Walloon region and 1.5 % of the population in Brussels) (Boffin et al., 2013). In 2021, the network included 96 SGPs (for 73 practices) covering 0.85 % of the Belgian population; 1.23 % in Brussels; 0.89 % in Flanders; 0.69 % in Wallonia. The population covered, which serves as the denominator in computing incidence rates, is estimated by dividing the sum of all patient encounters in the participating SGP by the mean number of patient encounters in Belgian general practice per inhabitant, provided by the NIHDI) (Boffin et al., 2013). The SGPs are fairly similar to non-sentinel GPs according to age-gender distribution and the population covered is representative of the general population. The validity of the disease registration has been assessed (Lobet et al., 1987; Boffin et al., 2017). Zona was defined as groups of vesicles which are localized on the area of one dermatome (International Classification of Primary Care, ICPC-2, code S70) (Sabbe et al., 2014). In addition to age and sex, other variables were also registered: being vaccinated against chickenpox, a history of chickenpox, duration of symptoms before consulting, treatment with antiviral drugs. and hospitalization (https://www.sciensano.be/en/network-generalpractitioners); since 2021 being vaccinated against Herpes Zoster (zona), existence of ophthalmic zona. From 2021, Post-Herpetic Neuralgia (PHN) was also recorded. The Sentinel Network registered the first consultation of a new episode of HZ, which, in combination with catchment population estimates, enabled estimates of the annual incidence rate of patients with HZ who visit a GP at least once. This system did not cover cases seen only by a specialist (e.g. dermatologists, geriatrists) or in emergency rooms. However, it is unlikely that this would have resulted in an underestimation of registered cases as a previous Belgian survey reported that 99 % of ambulatory cases of HZ visited a GP (Bilcke et al., 2012). Moreover, it seems reasonable to think that people not seeking any medical care for their HZ were likely to experience a very small burden, and therefore their contribution to the analysis is negligible. Data collected in 2021 might be affected by COVID-related crisis resulting in a decreasing in consultation and/or in SGPs' participation.

Data from year 2006 to 2012 were provided by Sciensano. Incidence estimates and 95 % CI were also directly provided by Sciensano (Sabbe et al., 2014) after being been standardized by age and sex distribution of the Belgian population. There were 4 843 cases registered between 2006 and 2012 (Sabbe et al., 2014). In 2021, there were 185 cases of shingles registered and 9 cases of HPN. There were 665 cases registered in 2012, which can be extrapolated to 41 562 cases in the all population (1.6 % of the Belgian population is covered). There were 185 cases of shingles registered in 2021, which can be extrapolated to 21 765 cases in the population (0.85 % of the Belgian population is covered).

In 2021, immunosuppression status was collected, among registered cases 10 concerned immunosuppressed patients, 9 for shingles (4.9 %) and 1 for PHN (11.1 %). No patients were vaccinated against varicella nor herpes zoster. Majority had a history for varicella, 72.4 % in case of consultation for shingles and 55.6 % in case of PHN.

1.4.2 Incidence of HZ

The annual incidence of HZ in Belgium was stable during the period 2006-2012, varying from 33.5 per 10 000 person-years (95 %CI 30.9; 36.3) in 2006 to 38.5 cases per 10 000 person-years (95 %CI 35.6; 41.5) in 2012. The incidence of HZ in 2021 was 16.8 cases per 10 000 person-years (95 %CI 14; 18.6).The incidence increased with increasing age.

Of note, because of relatively low number of cases in the highest age ranges, the annual incidence was much more variable in the age groups. The incidence of HZ was consistently higher in women than in men.

Year	Male	Female
	Inc. (95% CI)	Inc. (95% Cl)
2006	26.2 (23;29.8)	40.3 (36.3;44.5)
2007	38.4 (34.4;42.9)	47.4 (43,52.2)
2008	35.4 (31.7;39.5)	49.3 (45;54)
2009	34.1 (30.4;38.1)	45.8 (41.6;50.3)
2010	31 (27.3;35.1)	45 (40.6;49.8)
2011	35.2 (31.1;39.7)	46.6 (41.9;51.7)
2012	33.8 (30;37.9)	40.4 (36.3;44.7)
2021	11.8 (9.8;13.1)	21.9 (18.3; 24.2)

Data source & calculation: Sciensano, GP sentinel

Table: Incidence rate (by 10 000 population) of reported herpes zoster cases, 2006-2012 and 2021.

Incidence rate (per 10 000 contacts) of reported herpes zoster, by age-group, Belgium, 2006-2012 and 2021 (Sciensano):



1.4.3 Recurrent HZ

HZ seems to protect against subsequent HZ-episodes. The incidence of a subsequent episode is lower than that of the first HZ-episode. In the Shingle Prevention Study, the incidence of a subsequent HZ-episode in the placebo group was very low during the follow-up (3/1 000) (Oxman et al., 2005).

1.4.4 HZ-related hospitalisations

HZ-related admissions to hospital are difficult to quantify in a global context of avoiding hospital admission and trying to treat diseases in the ambulatory sector.

It is difficult to distinguish between HZ as a cause for admission and HZ that has arisen during hospitalisation. The hospitalization rate for primary - cause HZ in Belgium is on average 14.2/100 000 person-years, and increases with increasing age (see figure above) (Bilcke et al., 2012)

Similar limitations apply to the quantification of PHN-related admissions. PHN may require seeking specialist advice from numerous departments (neurology, anaesthesiology, internal medicine).

Immunosuppressive treatment and HZ affecting the CNS and eyes are also risk factors for hospitalisation (Yawn et al., 2007).

1.4.5 HZ-related mortality

HZ-related mortality is difficult to distinguish from the mortality that can be attributed to underlying predisposing factors such as conditions that compromise immunity (Dworking et al., 1998). Bilcke et al. estimate mortality from HZ at 0.068/100 000 person-years, but this is difficult given the unspecific nature of HZ related mortality and the inconsistency by which this is reported (Bilcke et al., 2012).

1.4.6 PHN

There is no uniform definition of PHN, the incidence of which is therefore difficult to determine. Depending on the selected time interval, the risk of PHN will be different. Pain that persists for 30, 60, 90, 120 or 180 days after HZ is found in 18-30 %, 13-18 %, 10 to 12.4 %, 8.4 % or 5 % of cases, respectively (Oxman et al., 2005).

The incidence of PHN in 2021 was 0.8 cases per 10 000 person-years (95 %CI 0.7- 0.9), respectively 0.5 (95 %CI 0.4; 0.6) for women and 0.3 (95 %CI 0.2; 0.3) cases per 10 000 person-years for men.

1.5 HZ-treatment

Topical HZ-therapy involves keeping the cutaneous lesions dry and clean and avoiding topical antibiotic and antiviral treatment.

The nucleoside-analogs acyclovir, famciclovir, and valacyclovir may be used in the treatment of HZ. If they are initiated within 72 hours after the onset of the HZ-skin rash, these antiviral agents will reduce the duration of viral dissemination and of lesion formation, the time to healing and the severity and duration of the acute HZ-induced pain (Dworking et al., 2007). In a Cochrane review published in 2014 (Chen N, 2014), the effectiveness of antiviral therapy was evaluated on PHN. Six RCTs with a total of 1211 participants were included and found no significant difference between acyclovir and control groups in the incidence of PHN four months after the onset of the acute herpetic rash. They concluded that there is high quality evidence that oral acyclovir does not reduce the incidence of PHN significantly. In addition, there is insufficient evidence to determine the effect of other antiviral treatments.

Acute HZ- and PHN-induced pain is treated by administering paracetamol, NSAIDs, tricyclic antidepressants, opiates, anticonvulsants, and topical analgesics (Dworking et al., 2007). If they fail to have any satisfactory effect, referral to specialised pain centres may be required.

1.6 Preventing VZV-transmission

People with HZ should avoid all contact with at-risk individuals (pregnant women, premature infants and immunocompromised people). Healthcare staff with HZ should not be assigned to work in neonatology and paediatrics, and they should not provide care to severely immunocompromised patients. They can attend to patients in other departments, provided the lesions are covered. All contact with pregnant women should be avoided (CDC, 2006).

The impact of varicella vaccination in the childhood remains controversial on the incidence or age distribution of HZ (Tanuseputro et al., 2011).

2 Vaccines

In Belgium, the following vaccines are registered for vaccination against Herpes Zoster:

- a live attenuated vaccine is registered, Zostavax® (MSD)
- a non-live adjuvanted recombinant subunit vaccine against Herpes Zoster, Shingrix® (GSK).

2.1 Zostavax® (MSD)

Link to EPAR Zostavax: https://www.ema.europa.eu/en/medicines/human/EPAR/zostavax

2.1.1 Composition and storage

The OKA/Merck strain was isolated in 1974 from a healthy Japanese child with varicella attenuated by serial passage at 34 ° in human and guinea pig cells. The strain had 42 single nucleotide polymorphism from the wild type (Oxman CID 2000).

Zostavax® (MSD) lyophilised preparation that contains the Oka/Merck strain of the live, attenuated VZV, which is also used in the varicella vaccine (Varivax®, Proquad®).

Reconstituted with the supplied solvents, each 0.65 ml dose of the vaccine contains at least 19 400 PFU (4.29 log₁₀) of the Oka/Merck VZV-strain produced on diploïd human cells (MRC-5). In comparison, Varivax® contains at least 1 350 PFU (3.13 log₁₀) and Proquad® at least 9 840 PFU (3.993 log₁₀).

The lyophilised HZ-vaccine must be stored at a temperature of \leq 15 °C in a freezer with monitoring. The vaccine should be reconstituted according to the manufacturer's instructions using only the solvent provided. The reconstituted vaccine should be protected from light and be administered as soon as possible (i.e. within 30 minutes following reconstitution). Stability under optimal storage conditions is as long as 18 months according to manufacturer's instructions.

2.1.2 Indication, administration and posology

Zostavax is used to vaccinate people aged 50 years or older, to prevent herpes zoster (also known as zoster or shingles) and the long-lasting nerve pain that may follow the disease (post-herpetic neuralgia).

Individuals should receive a single dose (0.65 mL). Compared with a single-dose regimen, two-dose vaccination did not increase VZV antibody responses among individuals aged \ge 70 y. Antibody persistence after 12 mo was similar with all three schedules (Vesikari et al., 2013).

The vaccine can be injected subcutaneously (SC) or intramuscularly (IM), preferably in the deltoid region. The vaccine should be administered subcutaneously in patients with severe thrombocytopenia or any coagulation disorder.

2.1.3 Concomitant administration

ZOSTAVAX can be administered concomitantly with inactivated influenza vaccine as separate injections and at different body sites. The concomitant use of ZOSTAVAX and a 23-valent pneumococcal polysaccharide vaccine resulted in reduced immunogenicity of ZOSTAVAX in a small clinical trial. However, data collected in a large observational study did not indicate increased risk for developing herpes zoster after concomitant use with other vaccines. No data are currently available regarding concomitant use with other vaccines. Concurrent administration of ZOSTAVAX and anti-viral medications known to be effective against VZV has not been evaluated.

2.1.4 Clinical efficacy

The phase 3 randomised, double-blind, placebo-controlled "Shingles Prevention Study" (SPS) assessed the efficacy of Zostavax® with 38 546 adults aged \geq 60 years who had once contracted varicella or who had resided in the US for \geq 30 years (Oxman et al., 2005). The median follow-up time of the study population after vaccination was 3.1 years. Overall vaccine efficacy (VE) for HZ prevention was 51% (95 %CI 44-58). VE declined however from 64 % among persons aged 60-69 years to 18 % for persons older than 80 years. PHN (defined as pain \geq 3/10 on a numerical pain scale for \geq 90 days after the onset of the HZ-rash) was reduced by 66.5 % (95 %CI 47.5-79.2). Burden of illness (BOI, average per study group for the severity of HZ (i.e., the area under the curve of pain severity vs. pain duration for each trial subject)) was reduced by 61% (95 %CI 51-69).

The Short-Term Persistence Substudy (STPS) was initiated after the SPS trial to assess persistence of vaccine efficacy each year through year 7 after vaccination (Schmader et al., 2012). The study re-enrolled 7320 vaccine and 6950 placebo recipients from the initial SPS trial. Analysis of vaccine efficacy in each year after vaccination for all 3 outcomes showed a decrease in vaccine efficacy after year 1, with a further decline thereafter. A statistically significant reduction of vaccine efficacy was observed after 5 years for the incidence of HZ and HZ BOI. Compared to the SPS trial, in the STPS, vaccine efficacy for HZ BOI decreased from 61.1 % [IC95 %:51.1-69.1] to 50.1 % [IC95 %:14.1-71.0], incidence of PHN from 66.5 % [IC95 %:47.5-79.2] to 60.1 % [IC95 %:-9.8-86.7] and incidence of HZ from 51.3 % [IC95 %:44.2-57.6] to 39.6 % [IC95 %:18.2-55.5].

In the Long-Term Persistence Substudy (LTPS) assessment was extended to 11 years postvaccination for 6867 SPS vaccine recipients. Compared to SPS, estimated vaccine efficacy in LTPS decreased from 61.1 % [IC95 %: 51.1-69.1] to 37.3 % [IC95 %:26.7-46.4] for the herpes zoster (HZ) burden of illness (BOI), from 66.5 % [IC95 %:47.5-79.2] to 35.4 % [IC95 %: 8.8-55.8] for incidence of postherpetic neuralgia, and from 51.3 % [IC95 %: 44.2-57.6] to 21.1 % [IC95 %:10.9-30.4] for incidence of HZ, and declined for all 3 outcome measures from 7 through 11 years postvaccination. Vaccine efficacy for the HZ BOI was significantly greater than zero through year 10 postvaccination, whereas vaccine efficacy for incidence of HZ was greater than zero only through year 8 and was no more statistically significant after that time.

In a "real life" retrospective cohort study (75 761 recipients compared to 227 283 matched unvaccinated persons) performed in Southern California from 2007 to 2009, among community-dwelling adults aged over 60 years, the incidence of HZ was reduced from 13 cases/1 000 persons/year in unvaccinated persons to 6.4 cases/1 000 persons years for vaccinated persons (Hazard Ratio: 0.45 [95 % CI: 0.42-0.48](Tseng et al., 2011).These results were observed in all age subgroups and individuals with chronic diseases. A reduction of ophthalmic HZ and rate of HZ related hospital stays were respectively reduced by 63 % (HR: 0.37 [95 % CI: 0.23-0.61]) and 65 % (HR: 0.35[[95 % CI: 0.24-0.51]).

In another general-population-based retrospective cohort study among 766 330 Medicare beneficiaries aged over 65 years between 2007 and 2009, with a low vaccine uptake (3.9 %), the incidence rate of HZ decreased from 10/1000 person-years among unvaccinated beneficiaries to 5.4 cases/1 000 persons years for the vaccinated group (reduction of 52 %) (Langan et al., 2013).

2.1.5 The immunogenicity of Zostavax®

The immunogenicity of Zostavax® was examined in a substudy of the "Shingles Prevention Study" and which involved 1 395 trial subjects (Oxman et al., 2005). Zostavax® induces VZV-specific immunity and enhances T-cell memory, as measured (by gpELISA, RCF and INF γ ELISPOT) after 6 weeks. The immune response is inversely proportional to the risk of developing HZ. There is no clear dose-response relationship between the vaccine and VZV-antibodies. The CMI-response peaks 1 to 3 weeks after vaccination and is greater for those aged 60-69 years than for those aged \geq 70 years. This enhanced CMI-response (RCF and INF γ ELISPOT) persists for 3 to 6 years.

2.1.6 Contraindications, precautions and concomitant administration

Allergies to vaccine components

Zostavax® is not to be administered to patients with a history of previous anaphylactic reaction to one the vaccine components, including neomycin and gelatine.

A neomycin allergy usually manifests as contact dermatitis. Neomycin-induced contact dermatitis is not in itself a contraindication to vaccination with Zostavax®.

Immunocompromised individuals

Zostavax® is not to be administered to people with congenital or acquired immunodeficiency:

- People with active leukaemia, lymphomas, or other malignancies affecting the bone marrow or lymphatic system. Zostavax® can be given to individuals in remission, provided they have received no chemotherapy or radiation therapy for at least 3 months.
- People undergoing a haematopoietic stem cell transplantation (CDC, 2006).
- People with AIDS, or other manifestations of HIV, including a CD4+ T-cell count of ≤ 200/mm³ or ≤ 15 % total lymphocytosis. If the T-cell count is over 200/mm³, Zostavax could be safely administered.
- People under immunosuppressive medication:
 - High-dose corticosteroids (≥ 20 mg/day prednisone or equivalent doses)
 ≥ 2 weeks.

Low-dose systemic corticosteroids (< 20 mg/day prednisone), short-term (< 14 days), topical or intra-articular (also steroid injections in tendons and bursae) corticotherapy are not considered sufficiently immunosuppressive to jeopardise the safety of vaccination with Zostavax®. Studies are currently being conducted on the safety, tolerability and immunogenicity of Zostavax® in the event of chronic systemic corticosteroid therapy (5 - 20 mg prednisone).

For the same reason, treatment with methotrexate ($\leq 0.4 \text{ mg/kg/week}$), azathioprine ($\leq 3.0 \text{ mg/kg/day}$) or 6-mercaptopurine ($\leq 1.5 \text{ mg/kg/day}$) is not considered a contraindication to vaccination with Zostavax®.

Special other situations:

- Vaccination is recommended 2 to 4 weeks before planned immunosuppression (Harpaz et al., 2008).
- People with a humoral immunity disorder (e.g. hypo- or dysgammaglobulinaemia) may receive the vaccine.
- People undergoing treatment with recombinant human immune modulators: Vaccination should be performed prior to initiating such therapy or at least 1 month after discontinuing it.
- For patients with systemic lupus erythematosus (SLE), an open label vaccination study has shown that Zostavax vaccination yielded a measurable immune response in this cohort of mild SLE patients on mild-moderate immunosuppressive medications. No herpetiform lesions or lupus flares were seen in this small cohort of patients. Excluded patients in that pilot study were : patients with SLEDAI>4, use of mycophenolatemofetil, cyclophosphamide, biologics, or > 10 mg prednisone daily (Guthridgeet al., 2013).
- Zostavax could be safely administered to adults **moderately** immunosuppressed such as rheumatoid arthritis or psoriasis receiving moderate doses of methotrexate, corticosteroids or tumor necrosis factor inhibitors (Oxman et al., 2010).

<u>Pregnancy</u>

Pregnant women are not to be vaccinated with Zostavax®. A pregnancy should be avoided until 4 weeks after vaccination. It is not known what the effects of Zostavax® are on the foetus. The wild-type VZV entails a small risk to the foetus (CDC, 2006); the risk linked to the Oka/Merck VZV is likely to be even lower. Most people will already have acquired antibodies against varicella prior to vaccination, which further curbs viral replication, thus reducing the risk to the foetus. If a pregnancy occurs within 4 weeks after having received the Zostavax® vaccine, it is advisable to seek specialist advice.

In most cases, the fact that Zostavax® was administered will not constitute grounds for a decision to terminate the pregnancy.

Previous HZ-episode

Although there are no data available yet for this group as regards the safety and efficacy of the vaccine, a history of HZ is not a contraindication to vaccination with Zostavax® (Yawn et al., 2007). Hope-Simpson, in 1965, when formulating the hypothesis of immunity to VZV induced by varicella, calculated that half of persons who lived to 85 years would experience an HZ episode but that only 1 % would experience a second episode. In the SPS study, only 2 cases of a second episode was observed among the 642 placebo recipients who developed a first HZ episode (Weinberg et al., 2009). Optimal timing of vaccination and effectiveness after a first episode remains controversial. Because similar cellular immune response to Zostavax® during the three years after vaccination compared to a HZ episode, we might recommend to delay vaccination at least three years after a first episode in immunocompetent persons (Cohen et al., 2013).

People receiving antiviral therapy

Antiviral medication targeted at herpes viruses (acyclovir, famciclovir and valacyclovir) should be stopped at least 24 hours before and not be resumed until at least 14 days after vaccination with Zostavax® (CDC, 2008).

People receiving blood derivatives

Zostavax® can be administered at any time (before, during and after) the administration of blood and blood derivatives.

High titres of VZV-antibodies remain after an episode of varicella and are found at the same concentrations in blood and blood derivatives (Levin et al., 2008).

Breastfeeding mothers

Notwithstanding the fact that the target population (aged ≥ 60 years) does not include breastfeeding mothers, vaccinating breastfeeding mothers is not contraindicated, as the Oka/Merck VZV is not found in breast milk (CDC, 2008).

Moderate to severe acute illness

As regards people with a severe acute illness, it is preferable to postpone vaccination with Zostavax® until they have recovered from the acute illness (CDC, 2008).

Risk of Oka/Merck transmission following vaccination with Zostavax®

No additional measures are necessary when a person who was vaccinated with Zostavax® comes into contact with someone with increased susceptibility to VZV, unless the vaccinee develops a varicella-like rash. In that case, standard contact measures apply. Oka/Merck transmission was not documented in the "Shingles Prevention Study" (CDC, 2008). The risk of severe disease through Oka/Merck-transmission is low, which means that there is no need to resort to specific immunoglobulins (Varizig[™]). If necessary, the antiviral agents that are available for the treatment of HZ may be used.

2.1.7 Adverse effects

Serious adverse events

The "Shingles Prevention Study" did not find any difference in serious adverse events between the vaccine group and the placebo group. An increased risk of serious adverse events (x 1.5; vaccine: 1.9 % vs. placebo 1.3 %, 95 % CI: 1-2.3) was observed in a substudy conducted with 6 616 trial subjects, putting the vaccine at a disadvantage. However, no causal link with the vaccination was found to exist in terms of timing or clinical presentation. The mortality rate and the number of hospitalisations were similar in both study groups (Oxman et al., 2005). In the STPS and the LTPS substudy, no serious adverse events that may be related to vaccination were reported during the follow-up (11 years) and the rate of death was also similar between vaccine recipients and placebo (an average of 1 deaths/100 person years).

Mild local and systemic adverse events

In the "Shingles Prevention Study", adverse events were recorded during the first 42 days following injection. Adverse events more frequently reported at the injection site (erythema, pain, tenderness, swelling, and pruritus) in the vaccine group (48.3 %) than in the placebo group

(16.6 %, P< 0.05). The risk of such local reactions was greater among 60-69 year-olds (58.3 %) than among \geq 70 year-olds (41.3 %). Most local reactions are mild and disappear within four days.

Less severe systemic adverse events were more frequent in the vaccine group (6.3 %) than in the placebo group (4.9 %, P< 0.05). No difference was observed between the two study groups as regards any post-vaccination fever (Oxman et al., 2005).

Systemic reactions were rare and slightly more frequently reported in the vaccination group and consisted mostly as headache (9.4 % versus 8.2 % respectively).

The numbers of subjects with elevated temperature (\geq 38.3oC [\geq 101.0oF]) within 42 days postvaccination were similar in the ZOSTAVAX and the placebo vaccination groups [27 (0.8 %) vs. 27 (0.9 %), respectively]. The following adverse experiences in the AE Monitoring Substudy of the SPS (Days 0 to 42 postvaccination) were reported at an incidence \geq 1 % and greater in subjects who received ZOSTAVAX than in subjects who received placebo, respectively: respiratory infection (65 [1.9 %] vs. 55 [1.7 %]), fever (59 [1.8 %] vs. 53 [1.6 %]), flu syndrome

(57 [1.7 %] vs. 52 [1.6 %]), diarrhoea (51 [1.5 %] vs. 41 [1.3 %]), rhinitis (46 [1.4 %] vs. 36 [1.1 %]), skin disorder (35 [1.1 %] vs. 31 [1.0 %]), respiratory disorder (35 [1.1 %] vs. 27 [0.8 %]), asthenia (32 [1.0 %] vs. 14 [0.4 %]).

Among 50-59 years recipients, rate of injection site adverse reactions were frequent (64 % in the vaccine group compared to 14% in the placebo group [difference of 49.5 % [IC95 % 48.4-50.6]) but severe site injection adverse reaction were very infrequent (0.7 % in the vaccine group compared to 0.1 % in the placebo group) [difference of 0.1 % [IC95 % - 1-3]].

Rashes induced by and transmission of the Oka/Merck VZV

In the SPS study, twenty individuals in the vaccine group (0.1 %) and 7 in the placebo group (0.04) %) developed a varicella-like rash at the injection site (P< 0.05). VZV PCR was negative in both groups.

A generalised, varicella-like rash appeared to the same extent in both study groups. HZ-rashes occurred less frequently in the vaccine group than in the placebo group.

Oka/Merck VZV could not be found in any of the cases in which a varicella-like rash developed. There is also no evidence pointing to Oka/Merck VZV-transmission to someone else (Oxman et al., 2005).

2.2 Shingrix® (GSK)

Link to EPAR Shingrix: https://www.ema.europa.eu/en/medicines/human/EPAR/shingrix

2.2.1 Composition and storage

Shingrix® (GSK) is an adjuvanted (AS01B) Herpes Zoster (HZ) vaccine containing a glycoprotein E (gE) antigen produced by recombinant DNA technology in Chinese Hamster Ovary cells. Shingrix is provided in a lyophilized form (white powder) in monodose vials (50 μ g/dose). The AS01B (liquid) Adjuvant System is provided in separate monodose vials (0.5 mL/dose). The content of the AS01B vial is used to reconstitute the content of the gE vial prior to intramuscular injection of Shingrix.

The AS01B Adjuvant System contains 50 μ g of each of the immune-enhancers Quillaja saponaria Molina fraction 21 (QS-21) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL) combined with liposomes.

The list of vaccine excipients contains:

- Powder (gE antigen): Sucrose, Polysorbate 80 (E 433), Sodium dihydrogen phosphate dihydrate (E 339), Dipotassium phosphate (E 340)
- Suspension (AS01B Adjuvant System): Dioleoyl phosphatidylcholine (E 322), Cholesterol, Sodium chloride, Disodium phosphate anhydrous (E 339), Potassium dihydrogen phosphate (E 340), Water for injections

The pharmaceutical form of the reconstituted vaccine is a liquid suspension for injection appearing opalescent, colorless to pale brownish liquid.

The shelf-life of the vaccine is 3 years.

After reconstitution, the vaccine should be used promptly; if this is not possible, the vaccine should be stored in a refrigerator ($2 \degree C - 8 \degree C$). If not used within 6 hours it should be discarded.

2.2.2 Indication, administration and posology

Shingrix is indicated for the prevention of herpes zoster and post-herpetic neuralgia in adults 50 years of age and older and in adults 18 years of age and older at increased risk of HZ.

Shingrix is given intramuscularly (IM) in two doses of 0.5ml given at least two months apart. In subjects who need a shorter schedule due to a planned immunosuppressive therapy, the second dose can be given 1 to 2 months after the initial dose.

2.2.3 Clinical efficacy and safety in immunocompetent individuals (pivotal ZOE-50 and ZOE-70 trials)

The prophylactic efficacy and safety of Shingrix in older, immunocompetent individuals was evaluated in two pivotal phase 3, randomized (1:1), observer-blinded, placebo-controlled, multicentre trials (Cunningham et al., 2016; Lal et al., 2015). Both trials were run in parallel and were judged high quality based on the Risk of Bias tool of the Cochrane collaboration (RoB 2). ZOSTER-006 (ZOE-50) was performed in adults 50 years of age or older (n=15,411) whereas ZOSTER-022 (ZOE-70) included adults 70 years of age or older (n=13,900). Both trials were funded by GSK. Nine additional publications pertaining to these 2 trials were included in evaluation of efficacy and safety (Willer et al., 2019).

Prevention of Herpes Zoster (HZ)

In individuals \geq 50 years (ZOE 50), the incidence rate of HZ was 0.3 per 1 000 person-years in the vaccination group and 9.1 per 1 000 person-years in the placebo recipients, with a vaccine efficacy of 97.2 % (95 % CI: 93.7 to 99.0; p<0.001) over a 3.2 years follow-up period. The vaccine efficacy was 91.3 % (95 % CI: 86.8 to 94.5; p<0.001) in individuals \geq 70 years (data pooled from ZOE-50 and ZOE-70). There was no significant difference in vaccine efficacy among the age groups (91.3 % in 70-79 years, 91.4 % in \geq 80 years). In order to prevent one case of HZ, the Number Needed to Vaccinate (NNV) was 36.4 (95 % CI: 31.9-42.2) in ZOE-50 (\geq 50 years) and 32.3 (95 % CI: 28.5-37.1) in ZOE-50/70 (pooled \geq 70 years).

The vaccine efficacy was also evaluated in various subgroups (selected medical conditions at enrolment; at least one potential immune mediated disorder (pIMD); frailty) in post-hoc analysis (pooled ZOE-50/70; low risk of bias) (Curran et al., 2021; Dagnew et al., 2021; Oostvogels et al., 2019). Overall the vaccine efficacy was high in all subgroups with only small differences noticed. Vaccine efficacy was also similar between males and females (Willer et al., 2019).

The protective effect against HZ waned moderately over the years as the vaccine efficacy after the second vaccination was 97.6 % during year 1, 92.0 % during year 2, 84.7 % during year 3, and 87.9 % during year 4 but confidence intervals overlapped (pooled ZOE-50/70; modified vaccinated cohort) (Cunningham et al., 2016). An open-labelled follow-up study (Zoster-049 or ZOE-LTFU) of the pooled ZOE-50/70 population reported a vaccine efficacy of 90.9 % (95 % CI: 88.2-93.2) after 7 years follow-up (Boutry et al., 2021). The authors report a trend toward a plateau with vaccine efficacy in year 6 being 84.9 % (95 % CI: 70.4-93.1) and in year 7 being 85.3 % (95 % CI: 71.3-93.3). The NNV over 7 years was 23.4 (95 % CI: 21.6-25.7). The monitoring of participants of the two trials is still ongoing. The risk of bias was unclear as only 50.6 % (7413 participants) of the 14,648 ZOE-50/70 participants were enrolled (Boutry et al., 2021).

Prevention of Post Herpetic Neuralgia (PHN)

The incidence of postherpetic neuralgia (PHN) was 0.1 per 1 000 person-years in the vaccination group and 1.2 per 1 000 person-years in the placebo group, for a vaccine efficacy of 88.8 % (95 % CI: 68.7 to 97.1 %; P<0.001) among adults 70 years of age or older (pooled ZOE-50/70) and 91.2 % (95 % CI: 75.9 to 97.7 %; P<0.001) among adults \geq 50 yr (Cunningham et al., 2016). Postherpetic neuralgia did not develop in any vaccine recipients younger than 70 years of age. The incidence of PHN among vaccine recipients (12.5 % and 9.6 %, respectively; p=0.54). Thus, the protection against PHN appeared to be driven by the lower incidence of HZ. The NNV to avoid one extra PHN over 3.8 years was 334.5 (95 % CI: 251.5-499.4) for individuals \geq 50 years and 261.2 (95 % CI: 188.2-426.5) for individuals \geq 70 years. Prevention of PHN was not evaluated in the follow-up study of ZOE-50/70 (ZOE-LTFU) (Boutry et al., 2021).

Prevention of other complications and hospitalisations

Other complications included HZ vasculitis, disseminated HZ, ophthalmic, neurologic, or visceral disease, and stroke if they were associated with a confirmed HZ case (Kovac et al., 2018). Incidence rate was low in both groups (0.0 per 1 000 person-year in vaccinated (only 1 case), and 0.4 per 1 000 person-years in placebo group). Shingrix reduced the risk of HZ-related complications other than PHN by 93.7 % (95 % CI: 59.5 to 99.9 %; p=0.0003) in participants \geq 50 years and by 91.6 % (95 % CI: 43.3 to 99.8 %; p=0.0035) in participants \geq 70 years, with high imprecision of results. When PHN and other complications were considered together, the vaccine efficacy was 91.3 % (95 % CI: 78.5 to 97.3 %; p<0.0001) in participants \geq 50 years and by 88.6 % (95 % CI: 71.2 to 96.5 %; p<0.0001) in those \geq 70 years. There were too few hospitalizations for carrying out a meaningful assessment (5 in placebo group) (Kovac et al., 2018).

Adverse events

No safety signals were detected. Local reactions (pain, swelling and redness) were more frequent after vaccine (81.5 % in ZOE-50 and 74.1 % in ZOE-70) compared to placebo (11.9 % in ZOE-50 and 9.9 % in ZOE-70). Most reactions were mild or moderate, with around 9.0 % of vaccine recipients reporting grade 3 (severe) local reactions, and of short duration (Cunningham et al., 2019; Lal et al., 2015; López-Fauqued et al., 2019). Systemic reactions (myalgia, fatigue, fever, shivering, headache, gastro-intestinal symptoms) were also more frequent after vaccine (66.1 % in ZOE-50 and 53.0 % in ZOE-70) compared to placebo (29.5 % in ZOE-50 and 25.1 % in ZOE-70), with between 6.0 % (ZOE-70) and 11.4 % (ZOE-50 grade 3 reactions Cunningham et al., 2019; Lal et al., 2015). The median duration of symptoms was 2 days (López-Fauqued et al., 2019).

Serious adverse events³ were reported throughout the study period. The incidence of SAEs was balanced between RZV and placebo, but higher in ZOE-70 (16.6 % and 17.5 %) compared to ZOE-50 (9.0 % and 8.9 %) (Cunningham et al., 2019; Lal et al., 2015; López-Fauqued et al., 2019).

It should be noted that the second dose compliance in ZOE-50 and ZOE-70 was respectively 95.6 % and 94.4 % in RZV recipients and 96.4 and 95.6 % in placebo recipients, so generally very high and balanced between RZV and placebo, despite high frequency of reactogenicity after vaccine (Cunningham et al., 2019; Lal et al., 2015).

³ Serious Adverse Events include adverse events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/incapacity or result in a congenital anomaly/birth defect. Other important medical events, based upon appropriate medical judgment, may also be considered Serious Adverse Events if a trial participant's health is at risk and intervention is required to prevent an outcome mentioned.

2.2.4 Clinical efficacy and safety of RZV in immunocompromised patients

Safety, reactogenicity and immunogenicity of RZV in immunocompromised patients ≥18 years was studied in 4 phase III RCTs. The four patient groups studied were patients who underwent a haematological stem cell transplantation (ZOE-HSCT) (Bastidas et al., 2019; Curran et al., 2019; Stadtmauer et al., 2021), patients with haematological malignancies (HM) (Dagnew et al., 2019), renal transplants (Vink et al., 2019) and solid malignancies (Vink et al., 2019). The trials were judged high quality based on the Risk of Bias tool of the Cochrane collaboration. We included also data from a phase 1/2 RCT in HIV patients (Berkowitz et al., 2015).

Globally, two doses RZV triggered a robust immune response in all groups of immunocompromised patients. In patients with autologous hematopoietic stem cell transplantation (HSCT), clinical vaccine efficacy was also assessed (Bastidas et al., 2019). During the 21 month follow-up, confirmed HZ episodes occurred in 49 RZV recipients (30.0 per 1 000 person-years) and 135 placebo recipients (94.3 per 1 000 person-years) of the modified vaccinated cohort, resulting in a vaccine efficacy of 68.2 % (95 % CI: 55.6-77.5). Vaccine efficacy against PHN was estimated to be 89.3 % (95 % CI: 22.5-99.8, p=0.02), with high imprecision of results.

Globally, the safety profile was acceptable in all group of immunocompromised patients, and quite comparable to what was observed in immunocompetent vaccinees, although the incidence of events, including SAEs, in all participants was higher than in ZOE-50/70 trials.

2.2.5 Real world vaccine effectiveness

Data from observational studies report vaccine effectiveness that is largely in line with that from RCTs.

Two retrospective cohorts of immunocompetent individuals \geq 50 years showed similar results to those from the RCTs, with an adjusted vaccine effectiveness against HZ of 85.5 % (95 % CI: 83.5-87.3) and 83.5 % (95 % CI: 74.9-89.2) (Sun et al., 2021). Lower vaccine effectiveness was reported in a mixed cohort of immunocompetent and immunocompromised patients aged 65 years and older (Izurieta et al., 2021), and in a small cohort of patients with inflammatory bowel disease aged 60 years and older (Khan et al., 2021).

Real-world data on prevention against Herpes Zoster Ophtalmicus (HZO) in three studies showed vaccine effectiveness of 93.3 % (95 % CI: 48.7-99.1) (Sun et al., 2021), 89.1 % (95 % CI: 82.9-93.0) (Lu et al., 2021), and 66.8 % (95 % CI: 60.7-72.0) (Izurieta et al., 2021). The first two studies were in immunocompetent patients, whereas the second was in a mixed population of immunocompetent and immunocompromised patients, which might explain the difference in results.

2.2.6 Safety in post-marketing experience

Early RZV safety monitoring findings are consistent with prelicensure clinical trial data. Serious adverse events were rare, and no unexpected patterns were detected.

Pyrexia was reported most frequently (1,034; 23.6 %). Other systemic symptoms, such as chills, headache, fatigue, and myalgia, were commonly reported, as were injection site reactions. Reported signs and symptoms were similar whether RZV was administered alone or in combination with other vaccines. Median interval from receipt of RZV to onset of signs or symptoms was 1 day (i.e., the day after vaccination) (Hesse et al., 2019).

Two observational studies reported on the risk of Guillain-Barré syndrome (GBS) following RZV vaccine in community-dwelling Medicare beneficiaries of 65 years or older (Goud et al., 2021). The relative risk for GBS in the RZV group compared to the ZVL group was 2.34 (95 % CI: 1.01-5.41, p=0.047). The second study consisted of a self-controlled case series

analysis of eligible RZV vaccinees with an incident GBS outcome during 6 months follow-up. An increased risk for GBS syndrome was observed in the risk window (42 days after vaccination) compared to the control window (RR=2.84; 95 % CI: 1.53-5.27, p=0.001), resulting in an attributable risk of 3 per million RZV doses (95 % CI: 0.62-5.64) (Goud et al., 2021).

Three reports on post-licensure safety surveillance in the United States were recently published (Hesse et al., 2018; Pirrotta et al., 2021; Tavares-Da-Silva et al., 2020). No unexpected patterns were detected in reports of adverse events or serious adverse events.

2.2.7 Co-administration with other vaccines

In four RCTs the co-administration of RZV with other vaccines was assessed for immunogenicity and safety, including the reduced-antigen-content diphtheria-tetanusacellular pertussis vaccine (Tdap) (Strevoza et al., 2019), Influenza (Schwarz et al., 2017), 13valent pneumococcal conjugate vaccine (PCV13) (Min et al., 2021), and 23-valent pneumococcal polysaccharide vaccine (PPSV23) (Marechal et al., 2018) in adults aged 50 years or older. Non-inferiority of co-administration was demonstrated for all vaccines. The safety profile was in all studies acceptable. An ongoing study will evaluate co-administration of RZV with a vaccine against COVID-19 (mRNA-1273).

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VII COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: <u>About us.</u>

All experts joined the working group *in a private capacity*. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: <u>conflicts of interest</u>).

The following experts were involved in drawing up and endorsing this advisory report. The working group was chaired by **Didier SCHOEVAERDTS**; the scientific secretary was Veerle Mertens.

BENSEMMANE Sherihane	Epidemiology	Sciensano
DE SCHEERDER Marie-	Internal medicine, Infectiology, Travel	UZ Gent
Angélique	clinic, HIV	
CALLENS Steven	Infectiology, Internal Medicine	UZ Gent
DOGNE Jean-Michel	Pharmacovigilance	UNamur, EMA
FLAMAING Johan	Geriatrics	UZ Leuven
GOVAERTS Frans	General medicine, Prevention and health promotion	Domus Medica
ROBERFROID Dominique	Epidemiology, Anthropology, Health sciences	KCE
ROSSI Camelia	Infectiology, internal medicine	CHU Ambroise Paré
SCHOEVAERDTS Didier	Geriatrics	CHU UCL Namur
STUBBE Muriel	Rheumatology	OLV Hospital Aalst
SWENNEN Béatrice	Epidemiology, Vaccinology	ULB
VAN LAETHEM Yves	Infectiology, Vaccinology, Travel medicine, HIV	CHU Saint-Pierre, ULB
ZEEVAERT Renate	Expert Clinical Evaluation	KCE

The following experts or administrations were heard but did not take part in endorsing the advisory report.

WUILLAUME Françoise Vaccine vigilance AFMPS-FAGG

The standing working group Vaccination (NITAG) discussed the advisory report at the NITAG meeting of May 12 2022 and approved the report by mail on July 18 2022. The standing working group was chaired by **Yves VAN LAETHEM**; the scientific secretariat were Veerle Mertens and Fabrice Péters. The following experts participated at the NITAG meeting and/or approval by mail.

BLUMENTAL Sophie	Paediatric Infectious Disease	HUDERF
BOIY Tine	Paediatrics	UZA
BRASSEUR Daniel	Paediatrics	ULB
CARILLO Paloma	General medicine, vaccination	ONE
CORNELISSEN Laura	Epidemiology, Obstetrics, Gynaecology	Sciensano
DE LOOF Geert	General medicine	BCFI

DE SCHEERDER Marie- Angélique	Internal medicine, Infectiology, Travel clinic, HIV	UZ Gent
DESMET Stefanie	Microbiology, Bacteriology	UZ Leuven
DOGNE Jean- Michel	Pharmacovigilance	UNamur, EMA
FRERE Julie	Pediatrics, Infectiology	CHU Liège
LEROUX-ROELS Isabel	Vaccinology, Infection prevention, Microbiology	UZ Gent
MAERTENS Kirsten	Vaccinology	UAntwerpen
MALFROOT Anne	Pediatrics, Infectiology	UZ Brussel
MICHIELS Barbara	General medicine	UAntwerpen
ROBERFROID Dominique	Epidemiology	KCE, UNamur
SCHOEVAERDTS Didier	Geriatrics	CHU UCL Namur
SPODEN Julie	General medicine	SSMG
SWENNEN Béatrice	Epidemiology, Vaccinology	ULB
TUERLINCKX David	Pediatrics, Vaccinology	CHU UCL Namur
VAN DAMME Pierre	Epidemiology, Vaccinology	UAntwerpen
VAN LAETHEM Yves	Infectiology, Vaccinology, Travel medicine, HIV	CHU Saint-Pierre, ULB
VEKEMAN Veerle	General medicine	Kind en Gezin
WAETERLOOS Geneviève	Quality of vaccines and blood products	Sciensano

The following experts or administrations were heard but did not take part in endorsing the advisory report.

DAEMS Joël	Directorate Drugs	RIZIV-INAMI
TOP Geert	Manager vaccination program	VAZG
WUILLAUME Françoise	Vaccine vigilance	AFMPS-FAGG

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About the Superior Health Council (SHC)

The Superior Health Council is a federal advisory body. Its secretariat is provided by the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC aims at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, staff members of scientific institutions, stakeholders in the field, etc.), 300 of whom are appointed experts of the Council by Royal Decree. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a Committee on Professional Conduct) as well as the final endorsement of the advisory reports by the Board (ultimate decision-making body of the SHC, which consists of 30 members from the pool of appointed experts). This coherent set of procedures aims at allowing the SHC to issue advisory reports that are based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

Once they have been endorsed by the Board, the advisory reports are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.hgr-css.be). Some of them are also communicated to the press and to specific target groups (healthcare professionals, universities, politicians, consumer organisations, etc.).

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