VACCINATION AGAINST HERPES ZOSTER VIRUS (ZONA)

JULY 2017
CSS No. 9209
In this scientific advisory report on public health policy, 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).
ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL N° 9209

Vaccination against Herpes Zoster

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This version was validated by the Board on July - 2017

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.

At this moment, one live attenuated vaccine is registered in Belgium for vaccination against Herpes Zoster, Zostavax® (MSD). GSK has also developed an inactivated vaccine against Herpes Zoster, Shingrix®. However, this vaccine is not yet registered in Belgium.

This report sets out the recommendations of the SHC on the use of the HZ-vaccine to prevent HZ and PHN.

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 RECOMMENDATIONS AND VACCINATION SCHEME

- Herpes Zoster (HZ) has an important burden of disease in Belgium and ageing is a strong risk factor. Therefore, the SHC advises that Zostavax® might be considered for individuals aged over 65 years.
- There is uncertainty on the best age-window and vaccination can be considered on an individual basis, while the advantages of a population based vaccination programme needs further clarification.
- Persons should be vaccinated by means of a single dose of Zostavax®. They are no date supporting administration of a second dose.
- People with a prior history of HZ and with chronic conditions (e.g., diabetes mellitus, chronic renal failure, COPD, RA) may be vaccinated, unless the underlying condition is a contraindication such as cellular immunodeficiency.
- A partial protection against HZ (Vaccine Efficacy [VE] of 52 %) and PHN (VE of 67 %) was demonstrated for 5 years after vaccination from 50 years to 79 years with the live-attenuated HZ Vaccine. However, protection is steadily decreasing over 10 years. After the age of 80 yrs there are no data on the efficacy.
- Zostavax® is not to be used in the treatment of acute HZ, the prevention of PHN in the event of acute HZ or the treatment of PHN. There is no need to enquire about a previous history of varicella or to carry out serological testing to verify the immunity status for varicella prior to administering Zostavax®.

These recommendations will be reviewed as soon as other vaccines arrive on the market or if there are additional data on the efficacy.

Taken all evidence in consideration, the SHC recommends that vaccination against HZ might be considered for all individuals between 65 and 79 years old. In case of immunosuppressive therapy, this vaccination could be considered from the age of 50 years old but if possible, at least 4 weeks before the start of the immunosuppressive therapy.

Secondary Effects

The live-attenuated HZ vaccine (Zostavax®) is safe and only minor injection-site related adverse events have been reported and headache as systemic side effect.

For a full description of the secondary effects of the vaccine Zostavax®, we refer to the public notice of the Federal Agency for Medicines and Health Products (FAMHP) and to the Center of Farmaceutotherapeutical Information of Belgium (BCFI/CBIP)

### Key words and MeSH terms

<table>
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<th>Keywords</th>
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<td>Erwachsene</td>
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<td>Postherpetische neuralgie</td>
<td>Névralgie post-herpétique</td>
<td>Postherpetische Neuralgie</td>
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2 MeSH (Medical Subject Headings) is the NLM (National Library of Medicine) controlled vocabulary thesaurus used for indexing articles for PubMed http://www.ncbi.nlm.nih.gov/mesh.
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2.7 Adverse effects

2.7.1 Serious adverse events

2.7.2 Mild local and systemic adverse events

2.7.3 Rashes induced by and transmission of the Oka/Merck VZV

(b) Shingrix® (GSK)  

V Conclusion and recommendations

1.1 Summary

1.2 Recommendations regarding the use of Zostavax®

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III  METHODOLOGY

Having assessed the request, the Board and the chairman of the study group identified the expertise needed. An ad-hoc study group was set up accordingly, containing experts from the following fields of expertise: Dermatology, Epidemiology, Infectiology, Geriatric Medicine, Vaccinology, General Medicine, Algology.

The group experts submitted a general declaration of interests and an ad-hoc statement and the potential for a conflict of interests has been assessed by the Committee for Deontology and Ethics.

The recommendations are based on an overview of the scientific literature, both from scientific journals and reports by national and international organisations with expertise in this matter (peer-reviewed), as well as the opinions of the experts.

Once approved by the study group, the recommendations were validated by the Board.

IV  ELABORATION AND ARGUMENTATION

Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
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<tr>
<td>AIDS</td>
<td>Acquired ImmunoDeficiency Syndrome</td>
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<tr>
<td>BOI</td>
<td>Burden Of Illness</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>CMI</td>
<td>Cell Mediated Immunity</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>DIC</td>
<td>Disseminated Intravascular Coagulation</td>
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<tr>
<td>gpELISA</td>
<td>Glycoprotein Enzyme-Linked ImmunoSorbent Assay</td>
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<tr>
<td>HAS</td>
<td>Haute Autorité de Santé</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HZ</td>
<td>Herpes Zoster</td>
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<td>INFγ ELISPOT</td>
<td>InterFeron γ Enzyme-Linked Immunospot</td>
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<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drug</td>
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<td>Polymerase Chain Reaction</td>
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<td>PHN</td>
<td>Postherpetic Neuralgia</td>
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<tr>
<td>QALY</td>
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<td>Rheumatoid Arthritis</td>
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<tr>
<td>RCF</td>
<td>Responder Cell Frequency</td>
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<td>SHC</td>
<td>Superior Health Council</td>
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<tr>
<td>VZV</td>
<td>Varicella Zoster Virus</td>
</tr>
<tr>
<td>VE</td>
<td>Vaccine efficacy</td>
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</table>
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 prodromen 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 ≥ 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, episcleritis, 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 nasociliary 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 et 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 Epidemiology

1.3.1 Risk factors for HZ and PHN

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

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).

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

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.

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).

1.3.2 Incidence of HZ and PHN

HZ

In Belgium, the incidence of HZ is between 38 and 46 per 10 000 person-years, with a higher incidence between the age of 70-79 years (Sabbe et al., 2012).

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).

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) (Blicke 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).
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).

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).
1.4 HZ-treatment

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

1.5 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

At this moment, one live attenuated vaccine is registered in Belgium for vaccination against Herpes Zoster, Zostavax® (MSD). GSK has also developed an inactivated vaccine (adjuvanted HZ subunit vaccine) against Herpes Zoster, Shingrix®. However, this vaccine is not yet registered in Belgium.

(a) Zostavax® (MSD)

2.1 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 diploid human cells (MRC-5).
In comparison, Varivax® contains at least 1 350 PFU (3.13 log_{10}) and Proquad® at least 9 840 PFU (3.993 log_{10}). For that reason, the minimum potency of HZ vaccine is 14 times greater than varicella vaccine. Each vaccine also contains antigenic material of nonviable Oka/Merck VZV.

Additional vaccine components are:
- sucrose
- hydrolysed pork gelatine
- NaCl
- monosodium L-glutamate
- dibasic sodium phosphate
- KCl
- Residual components of MRC-5 cells (including DNA and proteins).
- Potassium Dihydrogen phosphate
- Sodium hydroxyde
- Urea
- Small amounts of neomycin and calf bovine serum

The vaccine does not contain thimerosal or other preservatives. The lyophilised HZ-vaccine must be stored at a temperature of ≤ 15 °C in a freezer with monitoring. If the freezer is temporarily unavailable, the vaccine should be placed on dry ice in a suitable container that can be closed.

The solvent (water) should be stored separately at room temperature or in the refrigerator. 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.

2.2 Method of administration and posology

Zostavax® is given subcutaneously (SC) as a single dose of 0.65ml administered in the deltoid region of the upper arm. It should not be administered by intravascular or intramuscular (IM) injection. The syringes used for the vaccination must be free of preservatives, antiseptics and detergents so as not to inactivate the live attenuated Oka/Merck VZV. For patients with a severe thrombopenia or coagulation disorders, the subcutaneous route should be preferred.

A patient information statement is available on the following BCFI website: http://www.bcfi.be/nl/chapters/13?frag=20636

In a recent open-label randomised trial (Diez-Domingo et al., 2015) conducted in 354 subjects aged ≥ 50 years, intramuscular administration was compared to subcutaneous administration in terms of 4-week post-vaccination antibody titres measured by glycoprotein enzyme-linked immunosorbent assay (non-inferiority design). In adults aged ≥ 50 years, IM administration of Zostavax elicited similar immune responses to SC administration and was well tolerated, with fewer injection-site reactions than with SC administration. Systemic adverse events were comparable between groups. Injection-site reactions were less frequent with IM than SC route: erythema (15.9 % versus 52.5 %), pain (25.6 % versus 39.5 %) and swelling (13.6 % versus 37.3 %), respectively.
2.3 Concomitant administration

The immunogenicity of Zostavax® and that of the trivalent inactivated influenza vaccine remain unaffected when they are administered concomitantly (Kerzner et al.). There are no data available on the concomitant administration of other vaccines that are recommended for the elderly population. A study has been completed that assesses the immunogenicity of the vaccine when it is administered concomitantly with the 23-valent pneumococcal polysaccharide vaccine, but its results are not available yet. It can be said that the concomitant administration of live attenuated vaccines and inactivated vaccines does not result in a reduced immune response or additional adverse events. It follows that Zostavax® may be administered with other vaccines (e.g., Td, Tdap, 23-valent pneumococcal polysaccharide vaccine) during the same appointment (CDC, 2006).

Each vaccine should be administered at a separate site using different syringes. Zostavax® may be administered concomitantly with an inactivated vaccine. It is preferable to observe a 4-week waiting period before and after vaccination with another live attenuated vaccine when considering vaccination with Zostavax® (CDC, 2006).

2.4 Clinical efficacy

The phase 3 randomised, double-blind, placebo-controlled "Shingles Prevention Study" (SPS) assessed the efficacy of Zostavax® with 38 546 adults aged ≥ 60 years (median: 69.4 years; range: 50-99 years) who had once contracted varicella or who had resided in the US for ≥ 30 years (Oxman et al., 2005). The exclusion criteria for trial participation were the following:

- a history of HZ
- allergic sensitivity to one of the vaccine components
- conditions associated with impaired immunity
- conditions that would complicate the evaluations required in the study (e.g., life expectancy < 5 years, cognitive impairment, dermatological disorders, chronic pain, severe hearing loss and reduced mobility).

The median follow-up time of the study population after vaccination was 3.1 years. HZ was confirmed through PCR (93 %), culture (1 %) or by 5 HZ specialists (6 %).

The incidence of HZ and PHN (defined as pain ≥ 3/10 on a numerical pain scale for ≥ 90 days after the onset of the HZ-rash), and the 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)).

There were 315 cases of HZ in the vaccine group and 642 cases in the placebo group.

| TABLE 2: Efficacy of ZOSTAVAX® compared with a placebo, by age group — Shingles Prevention Study* |

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>No. subjects</th>
<th>HZ cases</th>
<th>PHN cases</th>
<th>% HZ cases with PHN</th>
<th>No. subjects</th>
<th>HZ cases</th>
<th>PHN cases</th>
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<td>44</td>
<td>3.7</td>
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</table>

* 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 available case of herpes zoster (HZ) within the first 30 days postvaccination.

* Age at randomization was age 60-69 years and ≥70 years.

** Postherpetic neuralgia (PHN) was defined as HZ-associated pain rated as three 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 onset of HZ rash using Zoster Brief Pain Inventory.

*** VZ for PHN and BOI calculated for the age groups 60-69 and ≥70 years.

Confidence interval.

* Age-adjusted estimate based on the age strata (age 60-69 years and ≥70 years) at randomization.

Zostavax® reduces the risk of HZ, the risk of PHN and the BOI by 51.3 %, 66.5 % and 61.1 %, respectively. The efficacy of Zostavax® against PHN rises from 58.9 to 72.9 % when the duration of pain used to define PHN is increased from 30 to 180 days. The vaccine reduced the incidence of PHN by 39 % in trial subjects who developed HZ.

The efficacy of Zostavax® in preventing HZ declines with increasing age (60-69 years: 64 % [IC95%: 56-71 %; 70-79 years: 41 % [IC95 %: 28-52]; ≥ 80 years: 18 % [IC95 %: -29-48 %]).

As regards the effect of Zostavax® on the BOI and the incidence of PHN, there are no significant age-related differences. VE on PHN was 65.7 % for the age-group 60-69 years [IC95 %: 20.4-86.7] and 66.8 for the age-group 70-79 (IC95 %: 43.3-81.3) (data not available for the age-group ≥ 80 years). VE on the burden of illness was 65.5 % for the age-group 60-69 years [IC95 %: 51.5-75.5] and 55.4 for the age-group 70-79 [IC95 %: 39.9-66.9] (data not available for the age-group ≥ 80 years).

The figure below shows how the efficacy of Zostavax® in preventing HZ and PHN evolves over time. These data have been extended to include a follow-up over 10 years (see below).

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 (7 5761 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 ophtalmic 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).
2.5 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 INFγ 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 ≥ 70 years. This enhanced CMI-response (RCF and INFγ ELISPOT) persists for 3 to 6 years.

2.6 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 (≤ 0.4 mg/kg/week), azathioprine (≤ 3.0 mg/kg/day) or 6-mercaptopurine (≤ 1.5 mg/kg/day) is not considered a contraindication to vaccination with Zostavax®.
  - 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 mycophenolate mofetil, cyclophosphamide, biologics, or > 10 mg prednisone daily (Guthridge et 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).

**Pregnancy**

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 were 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.
2.7 Adverse effects

2.7.1 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).

2.7.2 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 ≥ 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 (≥ 38.3°C ≥ 101.0°F) 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 ≥ 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 %]), diarrhea (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 unfrequent (0.7 % in the vaccine group compared to 0.1 % in the placebo group) [difference of 0.1 % [IC95 % - 1-3]].

2.7.3 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).

(b) Shingrix® (GSK)

An adjuvanted varicella-zoster virus (VZV) subunit vaccine has been developed by GSK, Shingrix®. Indeed, viral proteins are relatively poorly immunogenic and need to be co-administrated with an adjuvant to increase vaccine response rate (Coffman et al., 2010). VZV surface Protein E is the most immunogenic glycoprotein on the surface of VZV virions as well as VZV infected cells; in addition, it is the major target of anti VZV CD4 T cells and humoral response (Arvin, 1996). A recombinant VZV glycoprotein E was first tested in a phase II trial without adjuvant or with different doses of a liposome-based adjuvant of GSK, the AS01. (Other adjuvants AS03 and AS04 used in Influenza or HPV vaccines were shown less potent in priming cellular immunity against VZV than AS01) (Fochesato et al., 2016).

Two doses led to a higher immunogenic response than one dose, and adjuvanted formulations showed higher humoral and cellular immunogenicity (Chlibek et al., 2013). Interestingly, subjects older than 70 had an immunological response similar than those ≥ 50 years old.

In adjuvanted vaccines, local pain and fatigue (mostly mild) were the most frequent side effects and were more frequently encountered than in non adjuvanted formulations. In the subjects receiving 2 doses of the vaccine, this immune response persisted for up to 3 years (Chlibek et al., 2014).

After 6 years, humoral as well as cell mediated immunity had decreased by 20-25 % from month 36 but remained 4 (for cell mediated) to 7 times (for antibody mediated) higher than prevaccination (Chlibek et al., 2015). Interestingly, immunologic and safety data are available in 2 phases I/II studies of populations with a higher frequency and severity of shingles.

In autologous hematopoietic cell transplant recipients, an immune humoral and cellular response was elicited and persisted up to 1 year, at a level close to those of healthy adults ≥ 50 years old (Stadtmauer et al., 2014).

In HIV-infected adults, mostly receiving antiretroviral therapy, with CD4 T-cell count ≥ 200 cells/mm³, humoral and cellular response was also induced after 2 doses at a level comparable to those of healthy adults ≥ 50 years old. This response persisted at least until 18 months, without sustained impact on HIV viral load (Berkowitz et al., 2015).

Two large studies (The ZOE 50 study and the ZOE 70 study) on clinical efficacy of a 2 doses regimen (2 months apart) in healthy adults have been published, one in ≥ 50 years old and one in ≥ 70 years old (Lal et al., 2015; Cunningham et al., 2016).

In the ZOE 50 study, a randomized placebo controlled (RPC) phase III study in more than 15 000 participants older than 50 y (ZOE 50 study) and with a mean follow-up of 3,2 years, incidence of shingles was 0,3 % in the vaccinated group, versus 9,1 % in the placebo one (Lal et al., 2015). This led to a vaccine efficacy of 97,2 % [95 %IC:93.7-99.0], with no significant variation according to age (VE of 96.6 % [95 %IC:89.6-99.3] for the age group 50-59 years, 97.4 % [95 %IC:90.1-99.7] for the age group 60-69 and 97.9 % [95 %IC:87.9-100.0] for the age group over 70 years. Grade 3 symptoms (local or systemic) were noted in 17 % of vaccine recipients in contrast with 3,2 % of placebo recipients.

Recently, the results of the ZOE 70 study were recently published (Cunningham et al., 2016). In this RPC phase III study on 13 900 participants (mean age 75,6 y), incidence of shingles was 0,9% in the vaccinated group versus 9,2 % in the placebo one. The vaccination efficacy was similar between participants 70 to 79 years old (90 %) or ≥ 80 years old (89,1 %).

Pooling data from ZOE 50 and ZOE 70, a vaccine efficacy of 88,8 % was observed against postherpetic neuralgia.
V CONCLUSION AND RECOMMENDATIONS

1.1 Summary

HZ causes morbidity in 1/3 of the adult population. Its incidence, as well as that of PHN, increases with age.
In order to be effective, antiviral medication for the treatment of HZ needs to be initiated within 72 hours after the onset of the HZ-rash. This calls for promptly seeking medical attention in view of getting a diagnosis. The treatment in itself can only partially alleviate the pain and reduce the duration of HZ.
The symptoms of PHN cannot always be controlled through treatment. The elderly in particular are prone to the adverse effects of the analgesic medication that is used for PHN.

1.2 Recommendations regarding the use of Zostavax®

Zostavax was licensed by the FDA in 2005. In 2014, according to the HAS report, the following countries have funded HZ vaccination in a subset of old persons. Age for starting reimbursement vary according to the country ranging between 50 and 70 years.

<table>
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<th>FUNDING</th>
<th>Population</th>
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<tr>
<td>Australia</td>
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<tr>
<td>Sweden</td>
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WHO in June 2014 does not propose any recommendation for routine use of HZ vaccination due to insufficient data for the burden of disease, a waning effect with time and doubt for the best age-group who will benefit from vaccination program (http://www.who.int/wer).

In the United States, in August 2014, the Advisory Committee on Immunization Practices (ACIP) has updated their 2008-recommendations for use of HZ vaccine and propose a routine vaccination of all old persons over 60 years with a single dose of Zostavax.

In France, in October 2014, the Medical and Public Health Assessment Division has recommended routine vaccination in non-immunosuppressed adults aged 65 to 74 years with a single dose regimen. An additional recommendation was to include in the first year of starting the vaccination calendar to include also old persons aged 75-79 years.
In the Netherlands, the Health Council of the Netherlands has recently published a report in 2016 suggesting the lack of strong evidence regarding the potential benefits of HZ vaccination in a collective or public perspective; They conclude that vaccination against shingles is not eligible for inclusion in a public programme, such as the National Immunisation Programme. In UK, the vaccine is now routinely offered on the NHS as a single injection to people aged 70 and 78.

In conclusion:

- Herpes Zoster (HZ) has an important burden of disease in Belgium and ageing is a strong risk factor. Therefore, the SHC advises that Zostavax® might be considered for individuals aged over 65 years.
- There is uncertainty on the best age-window and vaccination can be considered on an individual basis, while the advantages of a population based vaccination programme needs further clarification.
- Persons should be vaccinated by means of a single dose of Zostavax®. They are no date supporting administration of a second dose.
- People with a prior history of HZ and with chronic conditions (e.g., diabetes mellitus, chronic renal failure, COPD, RA) may be vaccinated, unless the underlying condition is a contraindication such as cellular immunodeficiency.
- A partial protection against HZ (Vaccine Efficacy [VE] of 52 %) and PHN (VE of 67 %) was demonstrated for 5 years after vaccination from 50 years to 79 years with the live-attenuated HZ Vaccine. However, protection is steadily decreasing over 10 years. After the age of 80 yrs there are no data on the efficacy.
- Zostavax® is not to be used in the treatment of acute HZ, the prevention of PHN in the event of acute HZ or the treatment of PHN. There is no need to enquire about a previous history of varicella or to carry out serological testing to verify the immunity status for varicella prior to administering Zostavax®.

These recommendations will be reviewed as soon as other vaccines arrive on the market or if there are additional data on the efficacy.
VI REFERENCES


HRG/CSH aanbeveling voor varicella vaccinatie.


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: composition and mode of operation.

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: conflicts of interest).

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

<table>
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<td>BEUTELS</td>
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<td>UAntwerpen</td>
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The standing working group Vaccination has endorsed the advisory report. The standing working group was chaired by Yves VAN LAETHEM; the scientific secretary Veerle MERTENS.

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<td>THIRY</td>
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The following experts were heard but did not take part in endorsing the advisory report:
NEELS Pieter

The following administrations and/or ministerial cabinets were heard:

BERTHELS Nele AFMPS
BOELAERT Kristel Kind en Gezin
BRASSEUR Daniel AFMPS
CARRILLO ONE
SANTISTEVE Paloma ONE
CHEVALIER Pierre INAMI
DAEMS Joël INAMI
DE SCHUTTER Iris ZG
REYNDERS Daniel SPF SPSC
TOP Geert ZG
TREMERIE Jean-Marie COCOM
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 40 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.shc-belgium.be). Some of them are also communicated to the press and to specific target groups (healthcare professionals, universities, politicians, consumer organisations, etc.).

In order to receive notification about the activities and publications of the SHC, please contact: info.hgr-css@health.belgium.be.