PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

SHINGRIX

Herpes Zoster vaccine (non-live recombinant, $AS01_B$ adjuvanted)

Suspension for injection

Active immunizing agent

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4

Submission Control No: 200244 Date of Approval: October 13, 2017

Table of Contents

SHINGRIX

Herpes Zoster vaccine (non-live recombinant, $AS01_B$ adjuvanted)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength per 0.5 mL dose	Nonmedicinal Ingredients
Intramuscular injection	Suspension for injection/ 50 mcg Varicella Zoster Virus (VZV) glycoprotein E (gE)	Cholesterol, dioleoyl phosphatidylcholine, dipotassium phosphate, disodium phosphate anhydrous, polysorbate 80, potassium dihydrogen phosphate, *Quillaja saponaria* Molina, fraction 21 (QS-21), 3-O-desacyl-4'-monophosphoryl lipid A (MPL), sodium chloride, sodium dihydrogen phosphate dihydrate, sucrose, water for injections

DESCRIPTION

SHINGRIX is a sterile, non-live vaccine for intramuscular injection. The vaccine is supplied as a vial of lyophilized recombinant varicella zoster virus surface glycoprotein E (VZV gE) which is reconstituted at the time of use with the accompanying vial of $AS01_B$ adjuvant suspension.

INDICATIONS AND CLINICAL USE

SHINGRIX is indicated for prevention of herpes zoster (HZ, or shingles) in adults 50 years of age or older (see Clinical Trials section).

CONTRAINDICATIONS

Patients with a known hypersensitivity to the active substance or to any component of the vaccine. For a complete listing, see the Dosage Forms, Composition and Packaging section.

WARNINGS AND PRECAUTIONS

General

Prior to immunization
It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Precautions for use
Do not administer the vaccine intravascularly, intradermally or subcutaneously.

Maladministration via the subcutaneous route may lead to an increase in transient local reactions.

SHINGRIX is not indicated for prevention of primary varicella infection or for the treatment of herpes zoster (HZ) or postherpetic neuralgia (PHN).

Febrile Illness
As with other vaccines, vaccination with SHINGRIX should be postponed in subjects suffering from an acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

Hematologic
As with other vaccines administered intramuscularly, SHINGRIX should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

Syncope
Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Special Populations

Geriatrics (≥60 years of age): The efficacy and safety in subjects 60 years and older were assessed in clinical trials (see Clinical Trials section).

Pregnant Women: There are no data on the use of SHINGRIX in pregnant women. Animal studies performed with SHINGRIX administered to female rats do not indicate any harmful effects with respect to pregnancy (see Toxicology section).

Nursing Women: The effect on breast-fed infants of administration of SHINGRIX to their mothers has not been studied.

Pediatrics (<18 years of age): The safety and efficacy of SHINGRIX in individuals younger than 18 years have not been established.

Immunocompromised (IC) individuals (≥50 years of age): There are limited data available on the use of SHINGRIX in immunocompromised adults 50 years of age or older (see Clinical Trials section).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

More than 17,000 adults aged 50 through 96 years of age received at least one dose of SHINGRIX in 17 clinical studies. The incidence of solicited local and general symptoms was higher in subjects who received SHINGRIX than in subjects who received control (placebo or other vaccines). SHINGRIX was generally well tolerated.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The safety of SHINGRIX was evaluated by pooling data from two pivotal phase III placebo-controlled clinical studies, ZOE-50 (Zoster-006) and ZOE-70 (Zoster-022), involving 29,305 subjects aged 50 years and older who received at least one dose of SHINGRIX (n = 14,645) or placebo (n = 14,660) administered according to a 0- and 2-month schedule.

Solicited Adverse Events

The reported frequencies of solicited local and general adverse events from studies ZOE-50 and ZOE-70 are presented in Table 1.

Data on solicited local and general adverse events were collected using standardized diary cards for 7 days following each vaccine dose or placebo in a subset of subjects (n = 4,884 receiving SHINGRIX, n = 4,880 receiving placebo with at least one documented dose in the ZOE-50 and ZOE-70 studies).

Table 1 Percentage of subjects with solicited local adverse reactions and general adverse events within 7 days[a] of vaccination in adults aged 50 to 69 years and 70 years and older[b] (a subset of TVC with 7-day diary card) in studies ZOE-50 and ZOE-70

	Aged 50 - 69 Years		Aged ≥70 Years	
	SHINGRIX (%)	Placebo[g] (%)	SHINGRIX (%)	Placebo (%)
Local Adverse Reactions[e]	**n = 2626**	**n = 2617**	**n = 2258**	**n = 2263**
Pain	85.6	12.8	69.2	8.8
Redness	38.5	1.4	37.7	1.2
Swelling	28.5	0.9	23.0	1.1
General Adverse Events[f]	**n = 2624**	**n = 2617**	**n = 2252**	**n = 2264**
Myalgia	53.0	13.2	35.1	9.9
Fatigue	51.3	18.3	36.6	14.4
Headache	45.2	18.6	29.0	11.8
Shivering	33.1	6.5	19.5	4.9
Fever[c]	25.9	3.2	14.3	2.7
Gastrointestinal[d]	20.5	9.7	13.5	7.6

TVC = Total vaccinated cohort for safety included all subjects with at least one documented dose (n).
a 7 days included day of vaccination and the subsequent 6 days.
b Pooled data from ZOE-50 (subjects ≥50 years) and ZOE-70 (subjects ≥70 years).
c Fever defined as ≥37.5°C/99.5°F for oral, axillary, or tympanic route, or ≥38°C/100.4°F for rectal route
d GI = Gastrointestinal symptoms including nausea, vomiting, diarrhea, and/or abdominal pain.
e All solicited local (injection site) adverse reactions will be considered causally related to vaccination.
f Solicited general adverse events are those experiences which do not occur at the site of injection and are temporally associated with the use of the vaccine, whether or not considered related.
g Placebo = saline solution

The majority of solicited local adverse reactions and general adverse events seen with SHINGRIX were mild to moderate in intensity and were not long-lasting (median duration of 3 days).

The incidence of solicited local and general symptoms was numerically lower in subjects aged 70 years and older compared with those aged 50 to 69 years.

The incidence of solicited local adverse reactions and general adverse events of SHINGRIX from the ZOE-50 and ZOE-70 studies were generally the same following each dose.

Unsolicited Adverse Events

In studies ZOE-50 and ZOE-70, unsolicited adverse events that occurred within 30 days following each vaccination (Day 0 to 29) were recorded with diary cards in all subjects. In studies ZOE-50 and ZOE-70, unsolicited adverse events occurring within 30 days of vaccination were reported in 50.5% and 32.0% of subjects who received SHINGRIX (n = 14,645) and placebo (n = 14,660), respectively (Total Vaccinated Cohort). Unsolicited adverse events that occurred in ≥1% of recipients of SHINGRIX and at a rate at least 2-fold higher than placebo included chills (3.5% versus 0.2%), injection site pruritus (2.2% versus 0.2%), and malaise (1.7% versus 0.3%).

Serious Adverse Events (SAEs)

In studies ZOE-50 and ZOE-70, SAEs occurred at a similar rate in subjects who received SHINGRIX (2.3%) and placebo (2.2%) within 30 days after the last dose of vaccine or placebo. During the entire follow-up period (median 4.4 years, range: 0 to 5.0 years), SAEs were reported for 12.8% of subjects who received SHINGRIX and for 13.3% of subjects who received placebo. In both groups, the incidence of SAEs was higher in subjects aged 70 years and older compared with those aged 50 to 69 years. These events were either not in temporal association with vaccination and/or had alternative plausible causes.

Deaths

During the 30-day follow-up period, deaths were reported for 0.1% of subjects who received SHINGRIX and 0.1% of subjects who received placebo in studies ZOE-50 and ZOE-70. During the entire follow-up period (median 4.4 years, range: 0 to 5.0 years), deaths were reported in 4.3% of subjects who received SHINGRIX and in 4.6% of subjects who received placebo. Causes of death among subjects were consistent with those generally reported in adult and elderly populations. The majority of deaths were reported in subjects aged 70 years and older in the vaccine and placebo groups. None of the fatal cases were considered related to vaccination.

Potential Immune-Mediated Diseases

In studies ZOE-50 and ZOE-70, new onset of potential immune-mediated diseases (pIMDs) or exacerbation of existing pIMDs were reported for 1.2% of subjects who received SHINGRIX and 1.4% of subjects who received placebo during the entire follow-up period (median 4.4 years, range: 0 to 5.0 years). Approximately half of pIMDs occurred with time to onset longer than one year after the last vaccination. The most frequently reported pIMDs in the vaccine and placebo groups were polymyalgia rheumatica (0.2% in each group), rheumatoid arthritis (0.1% versus 0.2%, respectively), psoriasis (0.1% in each group), and autoimmune thyroiditis (0.1% in each group).

Flexible Dosing Schedule

In a phase III clinical study Zoster-026, where 119 adults ≥50 years of age were vaccinated with SHINGRIX following a 0, 6-month schedule, the safety profile was comparable to that observed in adults ≥50 years of age vaccinated with SHINGRIX following a 0, 2-month schedule (see Clinical Trials section).

Immunocompromised (IC) subjects

In studies Zoster-001 and Zoster-015, the co-primary objectives were to evaluate the safety and reactogenicity of HZ vaccine formulations in subjects ≥18 years of age (YOA) with a selected IC

condition (autologous Haematopoietic Cell Transplant (HCT) and HIV infection, respectively). More than half of the subjects who participated in Zoster-001 and Zoster-015 (54%) were ≥50 YOA. With the limited number of subjects (n =164), no safety concerns were identified as evaluated one year post-vaccination (see Clinical Trials section).

DRUG INTERACTIONS

Use with Other Vaccines

SHINGRIX can be given concomitantly with unadjuvanted seasonal influenza vaccine (see Clinical Trials section). The vaccines should be administered at different injection sites.

Drug-Drug Interactions
Interactions with drugs have not been established.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

- This medicinal product must not be mixed with other medicinal products.

Recommended Dosing
The primary vaccination schedule consists of two doses of 0.5 mL each; an initial dose at Month 0 followed by a second dose administered anytime between 2 and 6 months later. Administration of the second dose of SHINGRIX is important to ensure maximum vaccine efficacy and duration of protection against HZ disease.

The need for booster doses following the primary vaccination schedule has not been established.

Administration
SHINGRIX is for intramuscular injection only, preferably in the deltoid muscle.

Reconstitution
SHINGRIX is to be reconstituted only with the accompanying adjuvant suspension.

Use and Handling
The lyophilized powder and suspension should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not reconstitute the vaccine.

How to prepare SHINGRIX:

SHINGRIX must be reconstituted prior to administration.

1. Withdraw the entire contents of the vial containing the suspension into a sterile syringe.
2. Add the entire contents of the syringe into the vial containing the lyophilized powder.
3. Shake gently until the lyophilized powder is completely dissolved.

The reconstituted vaccine is an opalescent, colourless to pale brownish liquid.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not administer the vaccine.

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

Before administration:

1. Withdraw the entire contents of the vial containing the reconstituted vaccine into a sterile syringe.

2. Change the needle so that you are using a new needle to administer the vaccine.

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

OVERDOSAGE

No cases of overdosage have been reported.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Herpes Zoster Disease

Primary VZV infection results in varicella (chickenpox), after which VZV becomes latent in neurons of dorsal root and cranial nerve ganglia. HZ (or shingles) results from the reactivation of latent VZV in sensory ganglia.

Any person who has had varicella is at risk of developing HZ. Age is the most important risk factor for the development of HZ with two-thirds of the cases occurring in those over 50 years of age. The risk and severity of HZ is greatest in the elderly, an age group predicted to grow in coming decades. This age-related risk may be explained by waning immunity over time including the loss of components of VZV-specific cell mediated immunity as a result of natural aging processes. The severity of illness associated with HZ and its complications also increases markedly with age.

HZ can be a severely debilitating disease that typically presents as an acute, painful, vesicular rash distributed along a single dermatome. HZ rash is preceded by prodromal pain in 70% to 80% of the cases, and can last up to a week or longer. The prodromal pain might also be associated with fever, malaise and headache. During the eruptive phase, acute local neurological pain occurs in up to 90% of immunocompetent individuals. The median duration of acute phase pain is 2 weeks and can be very severe, disabling, and interfere with daily activities. The rash typically heals in 2-4 weeks but may leave scars or pigmentation changes. HZ-associated pain can persist for weeks, months or even years (see HZ Complications section).

The National Advisory Committee on Immunization (NACI) recommends herpes zoster vaccination. Refer to the NACI statement available on the Public Health Agency website for further information.

HZ Complications

By definition, HZ complications can only occur following HZ. HZ complications occur in approximately 25% of persons with HZ and become more common with age. The most common HZ complications are postherpetic neuralgia (PHN) and HZ ophthalmicus (HZO). PHN is defined as pain that persists for at least 3 months or occurs after the HZ rash itself has resolved. Affected patients report typical neurologic pain symptoms such as intermittent or continuous, deep or superficial throbbing or stabbing, spontaneous aching or burning, intense itching, allodynia, and hyperalgesia. PHN can only occur as a result of HZ and develops in 10% to 30% of patients, with approximately 30-50% of patients experiencing pain for >1 year and several studies have reported PHN lasting up to 10 years. HZO can develop when reactivation of VZV occurs in the ophthalmic division of the trigeminal nerve. Common manifestations of HZO include keratitis as well as other complications which can occur, including conjunctivitis, retinitis, optic neuritis and glaucoma. Chronic HZO may lead to pain, facial scarring and loss of vision.

Epidemiology

Nearly all adult Canadians (≥90%) have had chickenpox and are therefore at risk for HZ. HZ occurs most frequently among older adults and immunocompromised persons. In Canada, it has been estimated that 30% of the population will develop HZ at some point in their lives; this number increases to almost 50% for those who live to 85 years of age (YOA). Overall incidence rates range from 20 to 34 per 10,000 person-years, however they increase to 39 to 118 per 10,000 person-years in adults over 65 YOA. In Canada, PHN is estimated to occur in approximately 20% of adults after HZ onset overall, however it can increase to over 30% for those over 80 YOA.

Burden of disease and hospitalization rates have also been assessed across Canada and the estimated 130,000 new HZ infections would result in 252,000 physician consultations, 2,000 hospitalizations and 20 deaths annually.

Zoster-related hospitalization rates vary across Canada and have been estimated to range from 1.5 to 4.6 per 100,000 population for those aged 50-59 YOA, increasing with advancing age to reach as high as 75 per 100,000 population in those over 80 YOA as observed in an Ontario study conducted using administrative database data from 1992-2010.

Mechanism of Action

SHINGRIX is designed to induce antigen-specific cellular and humoral immune responses in individuals with pre-existing immunity against varicella zoster virus (VZV). Although no immunological correlate for protection against HZ has been identified, current knowledge suggests that VZV-specific cell-mediated immunity (CMI) is of primary importance in preventing HZ. VZV-specific antibodies (Abs) may help control viral dissemination and may thereby help limit the severity of HZ. While VZV-specific Abs may not be directly protective against HZ, they may represent an indirect measure of the CMI response to vaccination.

The antigen component of SHINGRIX is one of the major glycoproteins from VZV and is unable to replicate. When the vaccine antigen is combined with the $AS01_B$ Adjuvant System (composed of the plant extract *Quillaja saponaria* Molina, fraction 21 (QS-21) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL), the vaccine increases VZV-specific CMI, which is thought to be the mechanism by which it protects against zoster disease and its subsequent complications.

Non-clinical data show that the adjuvant component, $AS01_B$, induces a local and transient activation of the innate immune system through molecular pathways specific to MPL and QS-21, which act as immunoenhancers. This facilitates the recruitment and activation of antigen-presenting cells carrying gE-derived antigens in the draining lymph node, which in turn leads to the generation of gE-specific CD4+ T cells. The adjuvant effect of $AS01_B$ is the result of interactions between MPL and QS-21 formulated in liposomes. SHINGRIX also increases VZV-specific humoral immunity, which is an indicator of the responsiveness to the vaccine.

STORAGE AND STABILITY

For both lyophilized gE vial and adjuvant solution vial, store in a refrigerator (2°C to 8°C). Do not freeze. Store in the original package in order to protect from light.

For storage conditions after reconstitution of the vaccine, see Dosage and Administration, How to Prepare SHINGRIX section.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

SHINGRIX is a suspension for injection supplied as a single-dose vial of lyophilized glycoprotein E (gE) to be reconstituted with the accompanying vial of adjuvant suspension. A single dose after reconstitution is 0.5 mL.

The lyophilized powder is white. The suspension is an opalescent, colourless to pale brownish liquid.

Composition

After reconstitution, one dose (0.5 mL) contains:

Varicella Zoster Virus gE[1]	50 mcg
Quillaja saponaria Molina fraction 21 (QS-21)[2]	50 mcg
3-O-desacyl-4'-monophosphoryl lipid A (MPL)[2]	50 mcg

Additional Excipients

Powder (gE):
Dipotassium phosphate
Polysorbate 80
Sodium dihydrogen phosphate dihydrate
Sucrose

Suspension ($AS01_B$ Adjuvant System):
Cholesterol
Dioleoyl phosphatidylcholine
Disodium phosphate anhydrous
Potassium dihydrogen phosphate
Sodium chloride
Water for injections

[1] Varicella Zoster Virus (VZV) glycoprotein E (gE) produced by recombinant DNA technology in Chinese Hamster Ovarian cells

[2] The $AS01_B$ Adjuvant System is composed of the plant extract *Quillaja saponaria* Molina, fraction 21 (QS-21) (50 mcg) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* (50 mcg) combined with dioleoyl phosphatidylcholine (DOPC) (1 mg) and cholesterol (0.25 mg)

Packaging

SHINGRIX is available as two components:

- Single dose lyophilized gE in a vial (type I glass) with a stopper (butyl rubber), with brown caps
- Single dose adjuvant suspension in a vial (type I glass) with a stopper (butyl rubber), with blue-green caps

SHINGRIX is available in pack sizes (packaged without syringes or needles) of:

- 1 vial of lyophilized powder plus 1 vial of adjuvant suspension
- 10 vials of lyophilized powder plus 10 vials of adjuvant suspension

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Proper Name: Herpes Zoster vaccine (non-live recombinant, $AS01_B$ adjuvanted)

Product Characteristics

SHINGRIX is a sterile, non-live vaccine for intramuscular injection. The vaccine is supplied as a vial of lyophilized recombinant varicella zoster virus surface glycoprotein E (VZV gE) which is reconstituted at the time of use with the accompanying vial of $AS01_B$ adjuvant suspension.

The antigen in SHINGRIX is a truncate of the VZV gE expressed in Chinese Hamster Ovary cells presented in the form of a sterile white lyophilized powder. After purification, the non-infectious gE antigen component is formulated with excipients, filled into vials and lyophilized. The adjuvant suspension for SHINGRIX is an opalescent, colorless to pale brownish liquid supplied in vials.

The Adjuvant System, $AS01_B$, is composed of 3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* and a saponin molecule (QS-21) purified from plant extract *Quillaja saponaria* Molina, combined in a liposomal formulation. The liposomes are composed of dioleoyl phosphatidylcholine (DOPC) and cholesterol in phosphate-buffered saline solution containing disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium chloride, and water for injection.

CLINICAL TRIALS

Study demographics and trial design

Table 2 Summary of patient demographics for clinical trials

Study #	Trial design	Dosage, Route of Administration and Duration	Vaccinated Study subjects (n=number)[a] [# Canadian subjects enrolled*]	Mean age (Range)	Gender
Phase III Efficacy Studies					
ZOE-50 (Zoster-006)	Multi-centre, randomized, observer-blind, placebo-controlled in subjects 50 years of age and older	0.5 mL suspension IM injection 0, 2 months median follow-up: 3.1 years (range: 0 to 3.7 years)	15405 [α] (SHINGRIX n = 7695; placebo n = 7710) [629]	62.3 years (48 to 96 years)	61.1% female, 38.9% male
ZOE-70 (Zoster-022)	Multi-centre, randomized, observer-blind, placebo-controlled in subjects 70 years of age and older	0.5 mL suspension IM injection 0, 2 months median follow-up: 3.9 years (range: 0 to 4.5 years)	13900 [β] (SHINGRIX n = 6950; placebo n = 6950) [800]	75.5 years (62 to 96 years)	54.9% female, 45.1% male
Phase III Immunogenicity Studies					
Zoster-004	Multi-centre, randomized, open-label, controlled, co-administration with FLU D-QIV in subjects 50 years of age and older	SHINGRIX: 0.5 mL suspension IM injection, and/or 1 dose FLU D-QIV 0, 2 months Follow up : 12 months after last dose	SHINGRIX n = 828 [134]	63.4 years (50 to 92 years)	51.8% female, 48.2% male
Zoster-007	Multi-centre, randomized, double-blind, placebo-controlled in subjects 50 years of age and older (lot-to-lot consistency study)	0.5 mL suspension IM injection 0, 2 months Follow up : 12 months after last dose	SHINGRIX n = 651 [93]	64.5 years (49 to 91 years)	55.3% female, 44.7% male

Study #	Trial design	Dosage, Route of Administration and Duration	Vaccinated Study subjects (n=number)[a] [# Canadian subjects enrolled*]	Mean age (Range)	Gender
Zoster-026	Multi-centre, randomized, observer-blind, placebo-controlled in subjects 50 years of age and older	0.5 mL suspension IM injection 0, 2-month or 0, 6-month or 0, 12-month schedule Follow up : 12 months after last dose	SHINGRIX n = 354	64.2 years (50 to 86 years)	69.5% female, 30.5% male

IM = intramuscular
FLU D-QIV = GlaxoSmithKline's unadjuvanted quadrivalent seasonal influenza vaccine
* The number of Canadian subjects enrolled includes both placebo and vaccine subjects
$gE/AS01_E$ = 50 mcg gE plus ½ dose $AS01_B$ adjuvant
a Total number of clinical study subjects who received SHINGRIX = 16,738
α The total number of subjects randomised in study ZOE-50 = 16,161; number of subjects excluded from the TVC = 756; additional number of subjects excluded from mTVC: 652
β The total number of subjects randomised in study ZOE-70 = 14,816; number of subjects excluded from the TVC = 916; additional number of subjects excluded from mTVC: 737

Efficacy against Herpes Zoster (HZ)

In two large clinical studies, ZOE-50 and ZOE-70, SHINGRIX significantly reduced the risk of developing herpes zoster (HZ) when compared with placebo (Table 3 and Table 4).

Study ZOE-50 in Subjects 50 Years and Older
The efficacy of SHINGRIX against HZ in subjects ≥50 years of age (YOA) was evaluated in ZOE-50, a placebo-controlled, observer-blind clinical study conducted in 18 countries, from North America (US and Canada), Latin America, Europe, Asia, and Australia, in which 15,405 subjects received (randomized 1:1) two doses (0 and 2 months) of either SHINGRIX (n = 7,695) or placebo (n = 7,710) (see Table 2). The mean age of subjects was 62.3 years. Overall, 95.6% of subjects completed both doses of SHINGRIX in ZOE-50.

Subjects were followed for the development of HZ for a median of 3.1 years (range: 0 to 3.7 years). The study excluded, among others, subjects who were immunocompromised, had a previous history of HZ, were previously vaccinated against varicella or HZ, and patients whose survival was not expected to be at least 4 years, or with conditions that might interfere with study evaluations. Randomization was stratified by age: 50 to 59 years, 60 to 69 years, 70 to 79 years, and ≥80 years in a 8:5:3:1 ratio.

The primary endpoint was to evaluate vaccine efficacy in the prevention of HZ compared to placebo in adults ≥50 YOA, as measured by the reduction in HZ risk. Analyses were conducted when a pre-specified number of HZ cases accrued. Confirmed HZ cases were determined by either

Polymerase Chain Reaction (PCR) (89.4%), or by a Clinical Evaluation Committee (10.6%) when there were no samples available or with inconclusive PCR results. Individuals in both vaccine and placebo groups who developed HZ were evaluated and treated as per treating physician's judgment.

The primary efficacy results of the modified Total Vaccinated Cohort (mTVC), which includes subjects randomized in the study who received a second dose of the vaccine and did not develop a confirmed case of HZ within one month after the second dose, are presented in Table 3.

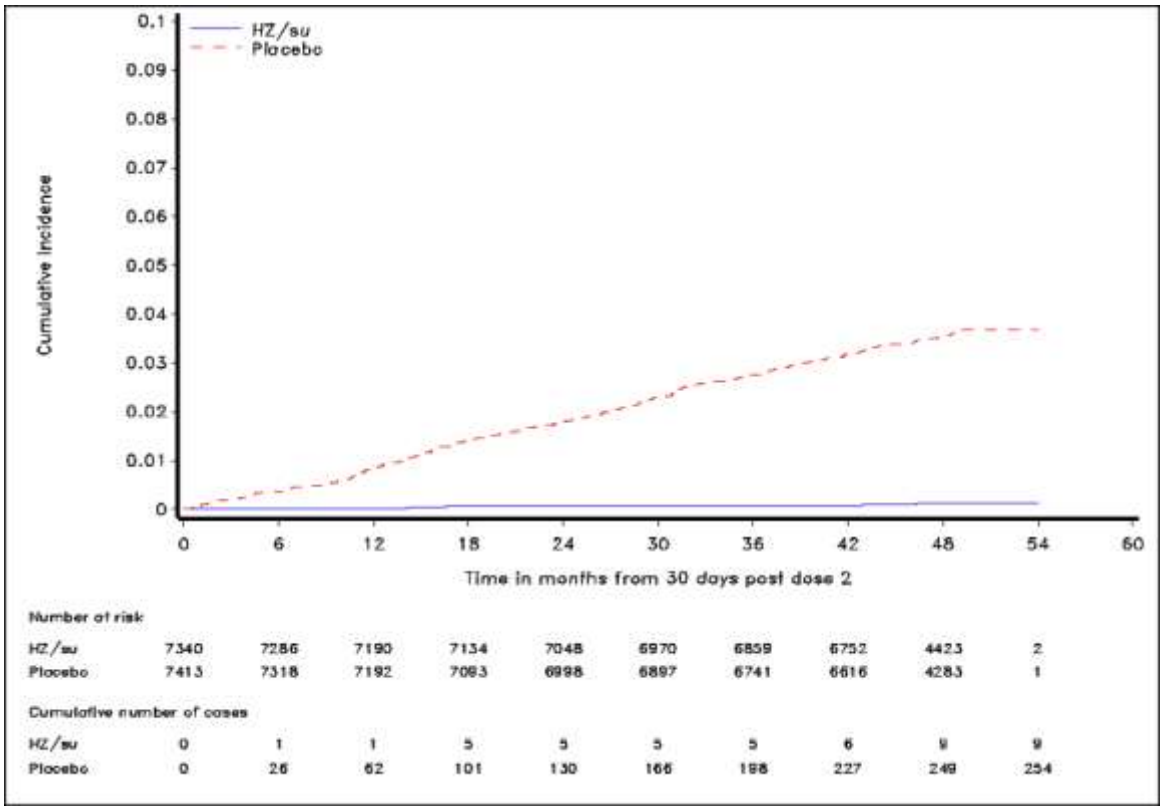
Table 3 Number of herpes zoster cases and vaccine efficacy on HZ incidence in subjects ≥50 YOA receiving two doses of SHINGRIX compared with placebo in study ZOE-50 (mTVC[a])

Age group (years)	SHINGRIX			Placebo			% Efficacy (95% CI)
	N	n	n/T (per 1000)	N	n	n/T (per 1000)	
Overall** (≥ 50)	7344	6	0.3	7415	210	9.1	97.2 (93.7, 99.0)
50 – 59*	3492	3	0.3	3525	87	7.8	96.6 (89.6, 99.4)
60 – 69*	2141	2	0.3	2166	75	10.8	97.4 (90.1, 99.7)
≥ 70*	1711	1	0.2	1724	48	9.4	97.9 (87.9, 100.0)

N = Number of subjects per group; n = Number of subjects having at least one confirmed HZ episode; CI = Confidence Interval
n/T (per 1000)= Incidence rate of subjects reporting at least one event
a Modified Total Vaccinated Cohort; the primary efficacy analysis which included all subjects randomized in the study who received a second dose of the vaccine and did not develop a confirmed case of HZ within one month after the second dose.
YOA = Years of age
(%) Efficacy = Vaccine Efficacy by Poisson method
* : VE adjusted by region
** : VE adjusted by age strata and region

SHINGRIX significantly reduced the risk of developing HZ by 97.2% (95% CI: 93.7, 99.0) in subjects ≥50 YOA as compared to placebo. The vaccine efficacy (VE) estimate was consistent regardless of the age of vaccination, including those ≥70 YOA. See also Figure 1.

Figure 1: Cumulative Incidence of Herpes Zoster over time in adults ≥50 YOA in the ZOE-50 study (mTVC)



In the fourth year after vaccination, vaccine efficacy against HZ in subjects ≥50 YOA in ZOE-50 was 93.1% (95% CI: 81.2, 98.2). The duration of protection beyond 4 years is currently under investigation.

Study ZOE-70 in Subjects ≥70 Years

ZOE-70 (Zoster-022) was a placebo-controlled, observer-blind clinical study, conducted in the same 18 countries as ZOE-50, in which 13,900 subjects aged 70 years and older received (randomized 1:1) two doses (at 0 and 2 months) of either SHINGRIX (n = 6,950) or placebo (n = 6,950). The mean age of subjects was 75.6 years (see Table 2). Overall, 94.4% of subjects completed both doses of SHINGRIX in ZOE-70.

Subjects were followed for the development of HZ and PHN for a median of 3.9 years (range: 0 to 4.5 years). The study exclusion criteria were the same as for ZOE-50. Randomization was stratified by age: 70 to 79 years and ≥80 years in a 3:1 ratio.

The primary objective was to evaluate VE in the prevention of HZ compared to placebo in adults ≥70 years of age (YOA), as measured by the reduction in HZ risk. The efficacy of SHINGRIX to prevent HZ in subjects ≥70 YOA was evaluated by combining the results from studies ZOE-50 and ZOE-70 through a pre-specified pooled analysis in the mTVC. A total of 8,250 and 8,346

subjects who received SHINGRIX and placebo, respectively, were included in the pooled mTVC analysis. Refer to Table 4.

Confirmed HZ cases were determined by either PCR (92.3%) or by a Clinical Evaluation Committee (7.7%).

The primary efficacy results of the modified Total Vaccinated Cohort (mTVC), which includes subjects randomized in the study who received a second dose of the vaccine and did not develop a confirmed case of HZ within one month after the second dose, are presented in Table 4.

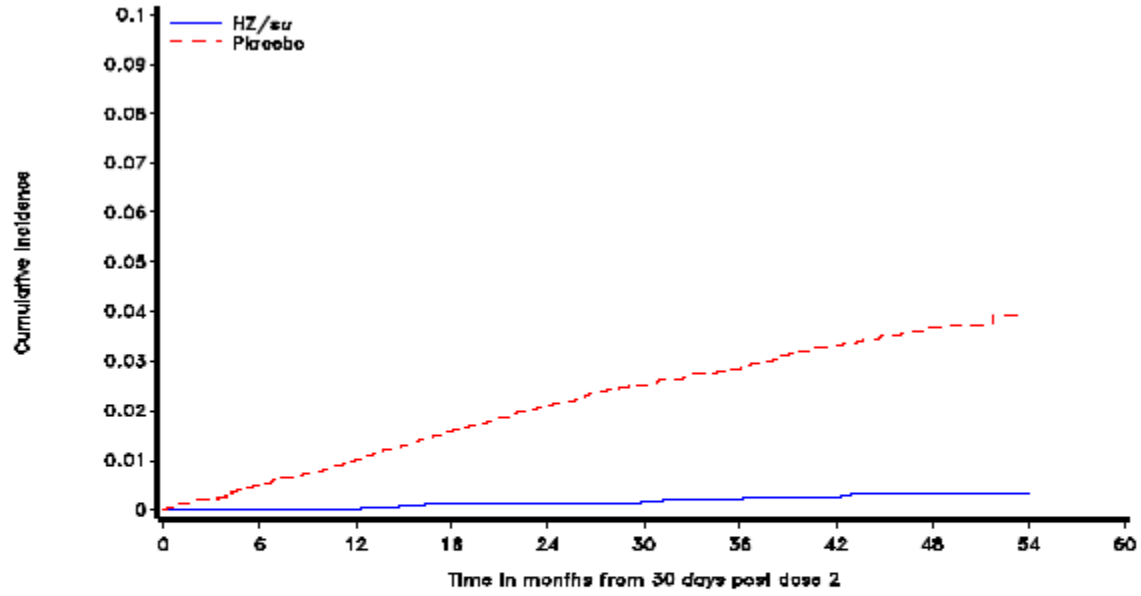
Table 4 Number of herpes zoster cases and vaccine efficacy on HZ incidence in subjects ≥70 YOA receiving two doses of SHINGRIX compared with placebo in studies ZOE-50 and ZOE-70 (Pre-Specified Pooled Data[a]) (mTVC[b])

Age group (years)	SHINGRIX			Placebo			% Efficacy (95% CI)
	N	n	n/T (per 1000)	N	n	n/T (per 1000)	
Overall** (≥ 70)	8250	25	0.8	8346	284	9.3	91.3 (86.8, 94.5)
70 – 79*	6468	19	0.8	6554	216	8.9	91.3 (86.0, 94.9)
≥ 80*	1782	6	1.0	1792	68	11.1	91.4 (80.2, 97.0)

N = Number of subjects per group; n = Number of subjects having at least one confirmed HZ episode; CI = Confidence Interval
n/T (per 1000)= Incidence rate of subjects reporting at least one event
a Pooled data from Study ZOE-50 (subjects ≥50 years) and Study ZOE-70 (subjects ≥70 years).
b mTVC = Modified Total Vaccinated Cohort; the primary efficacy analysis which included all subjects randomized in the study who received a second dose of the vaccine and did not develop a confirmed case of HZ within one month after the second dose.
YOA = Years of age
(%) Efficacy = Vaccine Efficacy by Poisson method
* : VE adjusted by region
** : VE adjusted by age strata and region

SHINGRIX significantly reduced the risk of developing HZ by 91.3% (95% CI: 86.8, 94.5) in subjects ≥70 YOA and by 91.4% (95% CI: 80.2, 97.0) in subjects ≥80 YOA, as compared to placebo. The VE estimate was consistent regardless of the age at immunization. See also Figure 2.

Figure 2: Cumulative incidence of herpes zoster over time in adults ≥70 YOA in the pre-specified pooled ZOE-50/-70 analysis (mTVC)



Number at risk										
HZ/su	8250	8164	8039	7923	7736	7623	7426	7247	3362	2
Placebo	8346	8213	8024	7869	7661	7493	7267	7080	3238	2
Cumulative number of cases										
HZ/su	0	0	2	7	9	13	18	20	25	25
Placebo	0	40	83	129	170	204	225	262	281	284

HZ/su = Herpes Zoster subunit vaccine
Placebo = Placebo

In the fourth year after vaccination, vaccine efficacy against HZ in subjects ≥70 YOA was 87.9% (95% CI: 73.3, 95.4). The duration of protection beyond 4 years is currently under investigation.

Pooled analysis of Study ZOE-50 and ZOE-70

Suspected HZ cases were followed prospectively for the development of PHN, a HZ-related complication defined as HZ-associated pain (rated as 3 or greater on a 0 to 10-point scale by the study subject) occurring or persisting at least 90 days following the onset of rash in evaluable cases of HZ using Zoster Brief Pain Inventory questionnaire.

The analysis of the overall rates of PHN in subjects ≥70 years of age (YOA) was conducted by combining the results from studies ZOE-50 and ZOE-70 through a pre-specified pooled analysis in the mTVC. A total of 8,250 and 8,346 subjects who received SHINGRIX and placebo, respectively, were included in the pre-specified pooled mTVC analysis. Table 5 compares the overall rates of PHN in SHINGRIX and placebo groups.

Table 5 Number of postherpetic neuralgia (PHN) cases and incidence rate in subjects ≥70 YOA receiving two doses of vaccine compared with placebo in studies ZOE-50 and ZOE-70 (Pre-Specified Pooled Data[a]) (mTVC[b])

Age group (years)	SHINGRIX			Placebo			% Efficacy (95% CI)
	N	n	Incidence Rate of PHN per 1,000 Person-Years	N	n	Incidence Rate of PHN per 1,000 Person-Years	
Overall (≥ 70)	8250	4	0.1	8346	36	1.2	88.8 (68.7, 97.1)
70 - 79	6468	2	0.1	6554	29	1.2	93.0 (72.4, 99.2)
≥ 80	1782	2	0.3	1792	7	1.1	71.2 (-51.6, 97.1)

N = Number of subjects per group; n = Number of subjects having at least one PHN; CI = Confidence Interval; PHN = Postherpetic neuralgia defined as HZ-associated pain rated as 3 or greater (on a 0-10 scale) occurring or persisting at least 90 days following the onset of rash using Zoster Brief Pain Inventory questionnaire.

YOA = Years of age

a Pooled data from Study ZOE-50 (subjects ≥50 years) and Study ZOE-70 (subjects ≥70 years).

b mTVC = Modified Total Vaccinated Cohort; the primary efficacy analysis which included all subjects randomized in the study who received a second dose of the vaccine and did not develop a confirmed case of HZ within one month after the second dose.

SHINGRIX significantly decreased the incidence of PHN compared with placebo in subjects ≥70 YOA (4 vs. 36 cases in the pre-specified pooled analysis of ZOE-50 and ZOE-70).

The benefit of SHINGRIX on PHN can be attributed to the effect of the vaccine on the prevention of HZ. A further reduction of PHN incidence in subjects with confirmed HZ could not be demonstrated due to the limited number of HZ cases in the vaccine group.

Effect on other HZ-related complications

A post-hoc pooled efficacy analysis to evaluate the overall VE in preventing HZ-associated complications (other than PHN), was performed on ZOE-50 and ZOE-70 including 27,916 subjects from the mTVC (n = 13,881 for SHINGRIX, n = 14,035 for placebo). The HZ-related complications evaluated were HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease, visceral disease, and stroke. The number of HZ-related complications other than PHN in subjects ≥50 YOA was 1 versus 16 cases in the SHINGRIX and placebo group, respectively.

Effect on Use and Duration of Pain Medication

In subjects ≥70 YOA from Study ZOE-70 with confirmed HZ, the use of HZ-associated pain medications was reported for 10 out of 23 subjects (43.5%) who received SHINGRIX, and for 160 out of 223 subjects (71.7%) who received placebo. The median duration of pain medication use was 30 (6.0-660.0) and 38 (1.0 and 4529.0) days, in the SHINGRIX group and the placebo group, respectively.

Immunological Evaluation

The gE-specific CD4+ T cell activity for cell-mediated immunity (CMI) was measured by intra-cellular cytokine staining (ICS) assay in terms of frequency of gE-specific CD4[2+] T-cells (i.e., CD4+ T cells expressing at least 2 activation markers from amongst IFN-γ, TNF-α, IL-2, and CD40-L) per 10^6 CD4+ T cells. Anti-gE antibody levels were measured by anti-gE enzyme-linked immunosorbent assay (gE ELISA). The vaccine response rate (VRR) for anti-gE was defined as the percentage of subjects with at least a 4-fold increase in post-Dose 2 anti-gE antibody concentration compared with the pre-vaccination anti-gE antibody concentration (for subjects seropositive at baseline) or with the anti-gE antibody cut-off value for seropositivity (for subjects seronegative at baseline). An immunological correlate of protection against HZ has not been established; therefore, the level of immune response that provides protection against HZ is unknown.

Immunogenicity in Dose Selection Study Zoster-003

The safety and immune response of SHINGRIX in adults 60 years of age (YOA) or older was evaluated in a dose selection study (Zoster-003). In study Zoster-003, there was an increase in CMI responses following the first dose of SHINGRIX, however, subjects who received a second dose of SHINGRIX developed a higher CMI response to gE after the second dose. In subjects in the SHINGRIX arm, the baseline median frequency of gE-specific CD4 T cells/10^6 cells was 122. This increased to 383 at two months post-Dose 1 (prior to dose 2) and to 1755 at one month post-Dose 2.

Humoral Immune Response

Humoral immune responses in subjects ≥50 YOA were evaluated in subjects from Study ZOE-50 who were randomly allocated to the immunogenicity subset (n = 1,197 for SHINGRIX and n = 1,200 for placebo). At one month post-Dose 2, the Geometric Mean Concentration (GMC) was 44.3-fold (95% CI: 41.7, 47.1) greater in subjects who received SHINGRIX compared with placebo.

Humoral immune responses in subjects ≥70 YOA were evaluated by combining the results from Studies ZOE-50 and ZOE-70 through a pre-specified pooled analysis in subjects from the immunogenicity subset (n = 1,646 for SHINGRIX and n = 1,647 for placebo). At one month post-Dose 2, the GMC was 35.4-fold (95% CI: 32.8, 38.1) greater in subjects who received SHINGRIX compared with placebo.

Anti-gE antibody responses with SHINGRIX were consistently high in all age groups at one month post-Dose 2 and remained above pre-vaccination levels at three years post-Dose 2.

Cell-Mediated Immune (CMI) Response

CMI responses to vaccination were evaluated in subjects from the immunogenicity subset of 3 countries in ZOE-50 (n = 232 for SHINGRIX and n = 234 for placebo). At one month post-Dose 2, the gE-specific CD4+ T cell activity in subjects who received SHINGRIX was 18.7-fold (95% CI: 14.0, 25.0) greater than placebo in subjects ≥50 YOA and 14.9-fold (95% CI: 8.8, 25.2) greater than placebo in subjects ≥70 YOA.

The gE-specific CMI responses with SHINGRIX were consistently above pre-vaccination levels in all age groups at one month post-Dose 2, and persisted relative to pre-vaccination levels through three years post-Dose 2.

Immunogenicity following concomitant vaccination
In a phase III, controlled, open-label clinical study (Zoster-004), 828 adults ≥50 years of age were randomized to receive 2 doses of SHINGRIX 2 months apart administered either concomitantly at the first dose (N=413) or non-concomitantly (N=415) with unadjuvanted seasonal quadrivalent influenza vaccine. The vaccine response rate (in terms of anti-gE antibodies) following co-administration of SHINGRIX with the influenza vaccine at 1 month post-dose 2 of SHINGRIX was 95.8% (95% CI: 93.3; 97.6). The antibody responses to both vaccines were similar, whether administered concomitantly or non-concomitantly.

Immunogenicity in subjects with a history of HZ prior to vaccination
In a phase III, uncontrolled, open-label clinical study (Zoster-033), 96 adults ≥50 years of age, with a history of HZ, received 2 doses of SHINGRIX 2 months apart. The vaccine response rate (anti-gE antibodies) at 1 month post-vaccination was 90.2% (95% CI: 81.7; 95.7).

Immunogenicity in subjects receiving 2 doses of SHINGRIX 6 months apart
In a phase III, open-label clinical study (Zoster-026) where 238 subjects ≥50 years of age were equally randomised to receive 2 doses of SHINGRIX 2 or 6 months apart, the vaccine response rate (anti-gE antibodies) at 1 month post-vaccination following the 0, 6-month schedule was 96.5% (95% CI: 90.4; 99.2).

The humoral immune response (anti-gE antibodies concentration) following the 0, 6-month schedule was not inferior to the humoral immune response following the 0, 2-month schedule, as the 97.5% CI upper limit of the antibodies concentration ratio was below 1.50 [1.16 (97.5% CI: 0.98; 1.39)].

Studies in Immunocompromised (IC) subjects

Study in autologous stem cell transplant subjects
A phase I/IIa study (Zoster-001) evaluated the safety, reactogenicity and immunogenicity of SHINGRIX and gE/AS01$_E$ study vaccine in IC subjects ≥18 YOA who were autologous Hematopoietic Cell Transplant (HCT) recipients. The study was stratified for underlying disease and subjects were randomized in a 1:1:1:1 ratio to receive one of 3 different immunization regimens. A total of 120 subjects were enrolled of which 96 were ≥50 YOA and received at least one vaccine dose (29 subjects in the 3-dose gE/AS01$_E$ group, 30 subjects in each of the 3-dose SHINGRIX and placebo groups and 31 subjects in the 2-dose SHINGRIX group), and 110 subjects completed the study, out of which 77 were ≥50 YOA.

With a limited number of subjects, the study showed that both the 3-dose and 2-dose regimens with SHINGRIX were immunogenic. No safety concerns were identified. The phase III efficacy study for HCT recipients is ongoing.

Study in HIV infected subjects

A phase I/IIa study (ZOSTER-015) evaluated the safety, reactogenicity and immunogenicity of SHINGRIX in the IC population of HIV-infected adults ≥18 YOA. Subjects were randomized according to a 3:2 ratio to receive 3 doses of SHINGRIX or placebo at 0, 2, 6 months. The study was stratified in 3 HIV-infected cohorts: An antiretroviral therapy (ART) High CD4 cohort (CD4+ T cell count ≥ 50 cells /mm^3 at screening), an ART Low CD4 cohort (CD4+ T cell count < 50 cells /mm^3 at screening), and a non-ART High CD4 cohort (CD4+ T cell count ≥ 500 cells/mm^3 at screening), with 94, 14 and 15 subjects in the respective cohorts. A total of 123 eligible subjects were vaccinated, of which 43 were ≥50 YOA (74 subjects in the 3-dose SHINGRIX group and 47 subjects in the placebo group), and 116 subjects completed the study, of which 42 were ≥50 YOA.

Data up to 1 month post last vaccination showed that SHINGRIX induced gE- and VZV-specific humoral and gE- and VZV-specific CMI responses post second dose and further increased modestly post third-dose. No apparent safety concern was identified with the limited number of subjects.

TOXICOLOGY

Reproductive Toxicology

Administration of VZV gE $AS01_B$ to female rats did not indicate any harmful effects with respect to fertility, pregnancy, embryo-foetal development, parturition or postnatal development.

Treatment of male rats did not affect mating performance, fertility or early embryonic development.

Animal toxicology and/or pharmacology

Non-clinical data reveal no special hazard for humans based on conventional studies of acute and repeated dose toxicity, local tolerance and cardiovascular/respiratory safety pharmacology.

REFERENCES

Chilbek, R., Smetana, J., Pauksens, K., Romboc, L., Anneke R., VH, Richardus, J., Plassmann G., Schwarz, T., Ledent,E., Heineman, T. 2014. Safety and immunogenicity of three different formulations of an adjuvanted varicella-zoster virus subunit candidate vaccine in older adults: A phase II, randomized, controlled study. Vaccine. 32: 1745-1753.

Cunningham et al., N Engl J Med 2016; 375: 1019-32. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older.

Lal et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. NEJM 2015;337:2087-96.

NACI, 2010. National Advisory Committee on Immunization (NACI) Statement. Statement on the Recommended Use of Herpes Zoster Vaccine. 2010. Published by the Public Health Agency of Canada. Accessed November 1, 2016. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-1/index-eng.php.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR VACCINE
PART III: PATIENT MEDICATION INFORMATION

SHINGRIX
Herpes Zoster vaccine (non-live recombinant, $AS01_B$ adjuvanted)
Suspension for Injection

Read this carefully before you receive **SHINGRIX**. This leaflet is a summary and will not tell you everything about this vaccine. Talk to your healthcare professional and ask if there is any new information about **SHINGRIX**.

What is SHINGRIX used for?
SHINGRIX is a vaccine that helps to protect adults against herpes zoster (also called shingles).

SHINGRIX can be given to adults 50 years and older.

What causes Shingles?
Shingles is caused by the same virus that causes chickenpox. After you have had chickenpox, the virus that caused it stays in your body in nerve cells. Sometimes, after many years and as you get older, the virus becomes active again and causes shingles. Anyone who has had chickenpox may get shingles and the chances of getting shingles increases as you get older. The lifetime risk of getting shingles is as high as 30% and this risk increases to almost 50% in those who live to 85 years.

What is Shingles?
Shingles is a serious disease that commonly results in a very painful, blistering rash. It usually occurs in one part of the body and can last for several weeks. Shingles sometimes also results in fever or headache. The pain can be severe, disabling and interfere with doing normal day-to-day activities.

If you develop shingles, it may lead to serious complications, such as long-lasting nerve pain (postherpetic neuralgia or PHN), which can last for months or years and may be severe even after the shingles blisters heal. Shingles can also lead to scarring. PHN is the most common complication you can develop if you have shingles. PHN can be serious, disabling, and can interfere with your daily activities such as walking, sleeping and social activities. The pain from shingles can also lead to emotional distress. People who suffer from shingles have described their pain in many ways. Some say the pain burns or throbs. Others say it stabs, shoots, and/or feels sharp. Severe pain can result from things as minor as a breeze or the touch of clothing against the skin. Other complications you may get with shingles can include bacterial skin infections, weakness, facial or muscle paralysis, loss of hearing or vision problems which can lead to blindness.

People with shingles may need to stay in the hospital and in rare cases shingles may even result in death.

How does SHINGRIX work?
SHINGRIX helps your body to build its own protection against shingles.

SHINGRIX was demonstrated to be more than 90% effective in preventing shingles in people who are 50 years or older, including those 70 to 80 years of age and older in clinical studies. SHINGRIX maintained protection for four years. The duration of protection beyond 4 years is currently under investigation.

As with all vaccines, SHINGRIX may not fully protect all people who are vaccinated.

What are the ingredients in SHINGRIX?

Medicinal ingredients:
1 dose (0.5 mL) contains 50 micrograms of glycoprotein E (gE) powder mixed with $AS01_B$ adjuvant suspension. gE is a protein found in the Varicella Zoster Virus. This protein is not infectious.

The adjuvant is made of 50 micrograms each of a plant extract (*Quillaja saponaria* Molina, fraction 21 (QS-21)) and a bacterial extract (3-O-desacyl-4'- monophosphoryl lipid A (MPL)) and is used to improve your body's response to the vaccine.

Non-medicinal ingredients:
Cholesterol, dipotassium phosphate, dioleoyl phosphatidylcholine, disodium phosphate anhydrous, polysorbate 80, potassium dihydrogen phosphate, sodium chloride, sodium dihydrogen phosphate dihydrate, sucrose and water for injections.

SHINGRIX comes in the following dosage forms:
0.5 mL suspension for one injection made by combining:
- One vial of gE powder
- One vial of adjuvant suspension

Do not use SHINGRIX if:
- You are allergic to any ingredient in SHINGRIX (see What are the Ingredients in SHINGRIX). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive SHINGRIX. Talk about any health conditions or problems you may have, including:
- If you have a severe infection with a high temperature. In these cases, vaccination may be delayed until recovery. A minor infection such as a cold should not be a problem, but talk to your healthcare professional first.
- If you have a bleeding problem or bruise easily.

- If you have fainted with a previous injection or before receiving any needle injection.

Other warnings you should know about:

SHINGRIX is not for prevention of chickenpox or for the treatment of herpes zoster (HZ) or postherpetic neuralgia (PHN).

Pregnancy and breast-feeding
- Ask your healthcare professional for advice before taking any medicine.
- There is no information on the use of SHINGRIX in pregnant or breast-feeding women.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines, or if you have recently received any other vaccine.

Using other medicines or vaccines with SHINGRIX:
- SHINGRIX can be given at the same time as the unadjuvanted seasonal influenza vaccine. The vaccines should be given at different injection sites.

How to receive SHINGRIX:
- SHINGRIX is given as an injection of 0.5 mL into a muscle (usually in the upper arm).

Usual dose:
You will receive two SHINGRIX injections with a gap of 2 to 6 months between doses. The first injection can be given from the age of 50 years. Your healthcare professional will tell you when you should come back for the second dose.

Make sure you receive both doses of SHINGRIX. This will maximise the protection offered by SHINGRIX.

Overdose:

If you think you have received too much SHINGRIX, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a scheduled injection, it is important that you make another appointment.

What are possible side effects from using SHINGRIX?

Like all medicines, SHINGRIX can cause side effects, although not everyone gets them. Most of the side effects experienced were mild to moderate and on average did not last longer than 3 days.

Very Common (these may occur with more than 1 in 10 doses of the vaccine):
- Pain, redness and swelling at the injection site
- Headache

- Stomach and digestive complaints (including nausea, vomiting, diarrhea and/or stomach pain)
- Muscle pain
- Tiredness
- Chills, fever

Common (these may occur with up to 1 in 10 doses of the vaccine):
- Injection site itching
- Generally feeling unwell

These are not all the possible side effects you may feel when taking SHINGRIX. If any of these side effects gets serious, or if you experience any side effects not listed here, contact your healthcare professional.

Reporting Suspected Vaccine Adverse Events
For the general public:
If you suspect you have had a serious or unexpected event following receipt of a vaccine, please ask your healthcare professional to complete the Adverse Events Following Immunization (AEFI) Form and send it to your local health unit in your province/territory.

For healthcare professionals:
If a patient experiences an adverse event following immunization, please complete the Adverse Events Following Immunization (AEFI) Form and send it to your local health unit in your province/territory.

If you have any questions or have difficulty contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:
Toll-free telephone: 1-866-844-0018
Toll-free fax: 1-866-844-5931
By email: caefi@phac-aspc.gc.ca
NOTE: Should you require information related to the management of the adverse events, please contact your health professional before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

Storage:
- Keep this vaccine out of the sight and reach of children
- Store in a refrigerator (2°C to 8°C)
- Do not freeze
- Store in the original package in order to protect from light
- Do not use this vaccine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.

If you want more information about SHINGRIX:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the latest available Patient Medication Information by visiting the Health Canada website; the manufacturer's website gsk.ca, or by calling 1-800-387-7374.

This leaflet was prepared by GlaxoSmithKline Inc.
Last Revised: October 13, 2017