

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Shingrix powder and suspension for suspension for injection  
Herpes zoster vaccine (recombinant, adjuvanted)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one dose (0.5 mL) contains:

Varicella Zoster Virus<sup>1</sup> glycoprotein E antigen<sup>2,3</sup> 50 micrograms

<sup>1</sup> Varicella Zoster Virus = VZV

<sup>2</sup> adjuvanted with AS01<sub>B</sub> containing:

plant extract *Quillaja saponaria* Molina, fraction 21 (QS-21) 50 micrograms

3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* 50 micrograms

<sup>3</sup> glycoprotein E (gE) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

### Excipients with known effect

Each dose contains 0.08 milligrams of polysorbate 80 (E 433) (see section 4.4).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and suspension for suspension for injection

The powder is white.

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

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Shingrix is indicated for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in:

- adults 50 years of age or older;
- adults 18 years of age or older at increased risk of HZ.

The use of Shingrix should be in accordance with official recommendations.

### 4.2 Posology and method of administration

#### Posology

The primary vaccination schedule consists of two doses of 0.5 mL each: an initial dose followed by a second dose 2 months later.

If flexibility in the vaccination schedule is necessary, the second dose can be administered between 2 and 6 months after the first dose (see section 5.1).

For subjects who are or might become immunodeficient or immunosuppressed due to disease or therapy, and whom would benefit from a shorter vaccination schedule, the second dose can be given 1 to 2 months after the initial dose (see section 5.1).

The need for booster doses following the primary vaccination schedule has not been established (see section 5.1).

Shingrix can be given with the same schedule in individuals previously vaccinated with live attenuated HZ vaccine (see section 5.1).

Shingrix is not indicated for prevention of primary varicella infection (chickenpox).

#### *Paediatric population*

The safety and efficacy of Shingrix in children and adolescents have not been established. No data are available.

#### Method of administration

For intramuscular injection only, preferably in the deltoid muscle.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

### **4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

#### Prior to immunisation

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

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

The vaccine is for prophylactic use only and is not intended for treatment of established clinical disease.

Shingrix should not be administered intravascularly or intradermally.

Subcutaneous administration is not recommended.

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

Shingrix should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following intramuscular administration to these subjects.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

There are no safety, immunogenicity or efficacy data to support replacing a dose of Shingrix with a dose of another HZ vaccine.

#### Excipients with known effect

##### *Polysorbate 80*

This medicinal product contains 0.08 mg of polysorbate 80 per dose. Polysorbates may cause allergic reactions.

##### *Sodium*

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

##### *Potassium*

This medicinal product contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially 'potassium-free'.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Shingrix can be given concomitantly with seasonal influenza vaccine (inactivated, unadjuvanted), 23-valent pneumococcal polysaccharide vaccine (PPV23), 13-valent pneumococcal conjugate vaccine (PCV13), reduced antigen diphtheria-tetanus-acellular pertussis vaccine (dTpa), coronavirus disease 2019 (COVID-19) messenger ribonucleic acid (mRNA) vaccine or respiratory syncytial virus (RSV) vaccine (recombinant, adjuvanted). The vaccines should be administered at different injection sites.

The adverse reactions of fever and shivering were more frequent when PPV23 vaccine was co-administered with Shingrix (16% and 21%, respectively) compared to when Shingrix was given alone (7% for both adverse reactions).

In adults aged 50 years and above, systemic adverse reactions that are very commonly reported (see Table 1; such as myalgia 32.9%, fatigue 32.2%, and headache 26.3%), and arthralgia, uncommonly reported, following administration of Shingrix alone were reported with increased frequency when Shingrix was co-administered with a COVID-19 mRNA vaccine (myalgia 64%, fatigue 51.7%, headache 39%, arthralgia 30.3%).

Concomitant administration of Shingrix with other vaccines than those listed above has not been studied.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

There are no data from the use of Shingrix in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Shingrix during pregnancy.

##### Breast-feeding

The effect on breast-fed infants of administration of Shingrix to their mothers has not been studied. It is unknown whether Shingrix is excreted in human milk.

## Fertility

Animal studies do not indicate direct or indirect effects with respect to fertility in males or females (see section 5.3).

### **4.7 Effects on ability to drive and use machines**

Shingrix may have a minor influence on the ability to drive and use machines in the 2-3 days following vaccination. Fatigue and malaise may occur following administration (see section 4.8).

### **4.8 Undesirable effects**

#### Summary of the safety profile

In adults aged 50 years and above, the most frequently reported adverse reactions were pain at the injection site (68.1% overall/dose; 3.8% severe/dose), myalgia (32.9% overall/dose; 2.9% severe/dose), fatigue (32.2% overall/dose; 3.0% severe/dose) and headache (26.3% overall/dose; 1.9% severe/dose). Most of these reactions were not long-lasting (median duration of 2 to 3 days). Reactions reported as severe lasted 1 to 2 days.

In adults  $\geq 18$  years of age who are immunodeficient or immunosuppressed due to disease or therapy (referred to as immunocompromised (IC)), the safety profile was consistent with that observed in adults 50 years and above. There are limited data in adults aged 18-49 years at increased risk of HZ who are not IC.

Overall, there was a higher incidence of some adverse reactions in younger age groups:

- studies in IC adults  $\geq 18$  years of age (pooled analysis): the incidence of pain at the injection site, fatigue, myalgia, headache, shivering and fever was higher in adults aged 18-49 years compared to those aged 50 years and above.
- studies in adults  $\geq 50$  years of age (pooled analysis): the incidence of myalgia, fatigue, headache, shivering, fever and gastrointestinal symptoms was higher in adults aged 50-69 years compared to those aged 70 years and above.

#### Tabulated list of adverse reactions

The safety profile presented below is based on a pooled analysis of data generated in placebo-controlled clinical studies on 5 887 adults 50-69 years of age and 8 758 adults  $\geq 70$  years of age. Of these 14 645 adults, 7 408 were included in a long-term follow-up extension study over a follow-up period of approximately 11 years after vaccination.

In clinical studies in IC adults  $\geq 18$  years of age (1 587 subjects) the safety profile is consistent with the data presented in Table 1 below.

Adverse reactions reported during post-marketing surveillance are also tabulated below.

Adverse reactions reported are listed according to the following frequency:

Very common	( $\geq 1/10$ )
Common	( $\geq 1/100$ to $< 1/10$ )
Uncommon	( $\geq 1/1\ 000$ to $< 1/100$ )
Rare	( $\geq 1/10\ 000$ to $< 1/1\ 000$ )
Very rare	( $< 1/10\ 000$ )

Within each frequency grouping the adverse reactions are reported in the order of decreasing seriousness.

**Table 1:** Adverse reactions

System Organ Class <sup>1</sup>	Frequency	Adverse reactions
Blood and lymphatic system disorders	Uncommon	lymphadenopathy
Immune system disorders	Rare	hypersensitivity reactions including rash, urticaria, angioedema <sup>2</sup>
Nervous system disorders	Very common	headache
	Very rare	Guillain-Barré syndrome <sup>3</sup>
Gastrointestinal disorders	Very common	gastrointestinal symptoms (including nausea, vomiting, diarrhoea and/or abdominal pain)
Musculoskeletal and connective tissue disorders	Very common	myalgia
	Uncommon	arthralgia
General disorders and administration site conditions	Very common	injection site reactions (such as pain, redness, swelling), fatigue, chills, fever
	Common	injection site pruritus, malaise

<sup>1</sup>According to MedDRA (medical dictionary for regulatory activities) terminology

<sup>2</sup>Adverse reactions from spontaneous reporting

<sup>3</sup> See 'Description of selected adverse reactions'

#### Description of selected adverse reactions

##### *Post-marketing observational studies of the risk of Guillain-Barré syndrome*

In 2 similar post-marketing observational studies in the US among individuals aged 65 years or older, an increased risk of Guillain-Barré syndrome (estimated 3 to 7 excess cases per million doses administered) was observed during the 42 days following any dose of Shingrix. In further analyses, the increased risk was observed following the first dose of Shingrix (estimated 6 to 12 excess cases of Guillain-Barré syndrome per million doses administered), but no increased risk was observed following the second dose.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system](#) listed in [Appendix V](#).

## **4.9 Overdose**

No case of overdose has been reported.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Vaccines, varicella zoster vaccines, ATC code: J07BK03

## Mechanism of action

By combining the VZV specific antigen (gE) with an adjuvant system (AS01<sub>B</sub>), Shingrix is designed to induce antigen-specific cellular and humoral immune responses in individuals with pre-existing immunity against VZV.

Non-clinical data show that AS01<sub>B</sub> induces a local and transient activation of the innate immune system through specific molecular pathways. 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<sup>+</sup> T cells and antibodies. The adjuvant effect of AS01<sub>B</sub> is the result of interactions between MPL and QS-21 formulated in liposomes.

## Clinical efficacy of Shingrix

### Efficacy against Herpes Zoster (HZ) and Post-Herpetic Neuralgia (PHN)

Two phase III, placebo-controlled, observer-blind efficacy studies of Shingrix were conducted in adults  $\geq 50$  years with 2 doses administered 2 months apart:

- ZOE-50 (Zoster-006): Total Vaccinated Cohort (TVC) of 15 405 adults  $\geq 50$  years who received at least one dose of either Shingrix (N=7 695) or placebo (N=7 710).
- ZOE-70 (Zoster-022): TVC of 13 900 adults  $\geq 70$  years who received at least one dose of either Shingrix (N=6 950) or placebo (N=6 950).

The studies were not designed to demonstrate efficacy in subgroups of frail individuals, including those with multiple comorbidities, although these subjects were not excluded from the studies.

Two phase III, placebo-controlled, observer-blind studies evaluating Shingrix efficacy were conducted in IC adults  $\geq 18$  years with 2 doses administered 1-2 months apart:

- Zoster-002: TVC of 1 846 autologous hematopoietic stem cell transplants (aHSCT) recipients who received at least one dose of either Shingrix (N=922) or placebo (N=924) 50-70 days post-transplant, 21.3% (Shingrix) and 20.5% (placebo) of the subjects received at least one immunosuppressive (IS) treatment (for a duration of at least one day) from HSCT up to 30 days after Dose 2 (TVC). The proportion of subjects by underlying disease was: 53.1% (Shingrix) and 53.4% (placebo) for multiple myeloma (MM) and 46.9% (Shingrix) and 46.6% (placebo) for other diagnosis.
- Zoster-039: TVC of 562 subjects with hematologic malignancies who received at least one dose of either Shingrix (N=283) or placebo (N=279) during a cancer therapy course (37%) or after the full cancer therapy course (63%). The proportion of subjects by underlying disease was: 70.7% (Shingrix) and 71.3% (placebo) for MM and other diseases, 14.5% (Shingrix) and 14.0% (placebo) for non-Hodgkin B-cell lymphoma (NHL) and 14.8% (Shingrix) and 14.7% (placebo) for chronic lymphocytic leukaemia (CLL).

These studies were not designed to assess the impact of concomitant use of IS therapy on vaccine efficacy or to assess the impact of specific IS treatments on vaccine efficacy. Most vaccine recipients were not under IS therapy at the time of vaccination (see above). Not all types of IS therapies were used in the populations studied.

Incidence of HZ and PHN cases as well as vaccine efficacy were evaluated in the modified Total Vaccinated Cohort (mTVC), i.e. excluding adults who did not receive the second dose of vaccine or who had a confirmed diagnosis of HZ within one month after the second dose.

Shingrix significantly decreased the incidence of HZ compared with placebo in:

- adults  $\geq 50$  years (ZOE-50): 6 vs. 210 cases;
- adults  $\geq 70$  years (pooled analysis of ZOE-50 and ZOE-70): 25 vs. 284 cases;
- adults  $\geq 18$  years with aHSCT (Zoster-002): 49 vs. 135 cases;
- adults  $\geq 18$  years with hematologic malignancies (Zoster-039): 2 vs. 14 cases. Vaccine efficacy was calculated post-hoc.

Vaccine efficacy results against HZ are presented in Table 2.

**Table 2:** Shingrix efficacy against HZ (mTVC)

Age (years)	Shingrix			Placebo			Vaccine efficacy (%) [95% CI]
	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1 000 person years	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1 000 person years	
ZOE-50*							
≥ 50	7 344	6	0.3	7 415	210	9.1	97.2 [93.7; 99.0]
50-59	3 492	3	0.3	3 525	87	7.8	96.6 [89.6; 99.4]
≥ 60	3 852	3	0.2	3 890	123	10.2	97.6 [92.7; 99.6]
60-69	2 141	2	0.3	2 166	75	10.8	97.4 [90.1; 99.7]
Pooled ZOE-50 and ZOE-70**							
≥ 70	8 250	25	0.8	8 346	284	9.3	91.3 [86.8; 94.5]
70-79	6 468	19	0.8	6 554	216	8.9	91.3 [86.0; 94.9]
≥ 80	1 782	6	1.0	1 792	68	11.1	91.4 [80.2; 97.0]
Zoster-002*** (aHSCT recipients <sup>#</sup> )							
≥ 18	870	49	30.0	851	135	94.3	68.2 [55.5; 77.6]
18-49	213	9	21.5	212	29	76.0	71.8 [38.7; 88.3]
≥ 50	657	40	33.0	639	106	100.9	67.3 [52.6; 77.9]
Zoster-039 (hematologic malignancy patients <sup>#</sup> )							
≥ 18	259	2	8.5	256	14	66.2	87.2**** [44.2; 98.6]

CI Confidence interval

\* Over a median follow-up period of 3.1 years

\*\* Over a median follow-up period of 4.0 years

Data in subjects ≥ 70 years of age are sourced from the pre-specified pooled analyses of ZOE-50 and ZOE-70 (mTVC) as these analyses provide the most robust estimates for vaccine efficacy in this age group.

\*\*\* Over a median follow-up period of 21 months

\*\*\*\* VE calculation was performed post-hoc; median follow-up period of 11.1 months

# antiviral prophylaxis in line with the local standard of care was permitted

Approximately 13 000 subjects with underlying medical conditions, including conditions associated with a higher risk of HZ, were enrolled in ZOE-50 and ZOE-70. Post-hoc analysis of efficacy against confirmed HZ undertaken in patients with common conditions (chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, depression or diabetes mellitus), indicates that the vaccine efficacy is aligned with the overall HZ efficacy.

Shingrix significantly decreased the incidence of PHN compared with placebo in:

- adults ≥ 50 years (ZOE-50): 0 vs. 18 cases;
- adults ≥ 70 years (pooled analysis of ZOE-50 and ZOE-70): 4 vs. 36 cases;
- adults ≥ 18 years with aHSCT (Zoster-002): 1 vs. 9 cases.



Vaccine efficacy results against PHN are presented in Table 3.

**Table 3:** Shingrix efficacy against PHN (mTVC)

Age (years)	Shingrix			Placebo			Vaccine efficacy (%) [95% CI]
	Number of evaluable subjects	Number of PHN* cases	Incidence rate per 1 000 person years	Number of evaluable subjects	Number of PHN* cases	Incidence rate per 1 000 person years	
ZOE-50**							
≥ 50	7 340	0	0.0	7 413	18	0.6	100 [77.1; 100]
50-59	3 491	0	0.0	3 523	8	0.6	100 [40.8; 100]
≥ 60	3 849	0	0.0	3 890	10	0.7	100 [55.2; 100]
60-69	2 140	0	0.0	2 166	2	0.2	100 <sup>§</sup> [< 0; 100]
Pooled ZOE-50 and ZOE-70***							
≥ 70	8 250	4	0.1	8 346	36	1.2	88.8 [68.7; 97.1]
70-79	6 468	2	0.1	6 554	29	1.2	93.0 [72.4; 99.2]
≥ 80	1 782	2	0.3	1 792	7	1.1	71.2 <sup>§</sup> [< 0; 97.1]
Zoster-002**** (aHSCT recipients <sup>#</sup> )							
≥ 18	870	1	0.5	851	9	4.9	89.3 [22.5; 99.8]
18-49	213	0	0.0	212	1	2.2	100.0 <sup>§</sup> [< 0; 100.0]
≥ 50	657	1	0.7	639	8	5.8	88.0 [10.4; 99.8]

\* PHN was defined as zoster-associated pain rated as ≥ 3 (on a 0-10 scale), persisting or appearing more than 90 days after onset of zoster rash using Zoster Brief Pain Inventory (ZBPI)

CI Confidence interval

\*\* Over a median follow-up period of 4.1 years

\*\*\* Over a median follow-up period of 4.0 years

Data in subjects ≥ 70 years of age are sourced from the pre-specified pooled analyses of ZOE-50 and ZOE-70 (mTVC) as these analyses provide the most robust estimates for vaccine efficacy in this age group.

\*\*\*\* Over a median follow-up period of 21 months

§ Not statistically significant

# antiviral prophylaxis in line with the local standard of care was permitted

The benefit of Shingrix in the prevention of 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.

In the fourth year after vaccination, the efficacy against HZ was 93.1% (95% CI: 81.2; 98.2) and 87.9% (95% CI: 73.3; 95.4) in adults ≥ 50 years (ZOE-50) and adults ≥ 70 years (pooled ZOE-50 and ZOE-70), respectively.

In Zoster-002, during a follow-up period starting 1 month post-dose 2 (i.e. corresponding to approximately 6 months after aHSCT) until 1 year after aHSCT, when the risk for HZ is the highest, the efficacy against HZ was 76.2% (95% CI: 61.1; 86.0).

#### Efficacy against HZ-related complications other than PHN

The evaluated HZ-related complications (other than PHN) were: HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease including stroke, and visceral disease. In the pooled analysis of ZOE-50 and ZOE-70, Shingrix significantly reduced these HZ-related complications by 93.7% (95% CI: 59.5; 99.9) and 91.6% (95% CI: 43.3; 99.8) in adults  $\geq 50$  years (1 vs. 16 cases) and adults  $\geq 70$  years (1 vs. 12 cases), respectively. No cases of visceral disease or stroke were reported during these studies.

In Zoster-002, Shingrix significantly reduced HZ-related complications by 77.8% (95% CI: 19.0; 96.0) in aHSCT recipients  $\geq 18$  years (3 vs. 13 cases).

In addition, in Zoster-002, Shingrix significantly reduced HZ-related hospitalisations by 84.7% (95% CI: 32.1; 96.6) (2 vs. 13 cases).

#### Effect of Shingrix on HZ-related pain

Overall in ZOE-50 and ZOE-70, there was a general trend towards less severe HZ-related pain in subjects vaccinated with Shingrix compared to placebo. As a consequence of the high vaccine efficacy against HZ, a low number of breakthrough cases were accrued, and it was therefore not possible to draw firm conclusions on these study objectives.

In subjects  $\geq 70$  years with at least one confirmed HZ episode (ZOE-50 and ZOE-70 pooled), Shingrix significantly reduced the use and the duration of HZ-related pain medication by 39.0% (95% CI: 11.9; 63.3) and 50.6% (95% CI: 8.8; 73.2), respectively. The median duration of pain medication use was 32.0 and 44.0 days in the Shingrix and placebo group, respectively.

In subjects with at least one confirmed HZ episode, Shingrix significantly reduced the maximum average pain score versus placebo over the entire HZ episode (mean = 3.9 vs. 5.5, P-value = 0.049 and mean = 4.5 vs. 5.6, P-value = 0.043, in subjects  $\geq 50$  years (ZOE-50) and  $\geq 70$  years (ZOE-50 and ZOE-70 pooled), respectively). In addition, in subjects  $\geq 70$  years (ZOE-50 and ZOE-70 pooled), Shingrix significantly reduced the maximum worst pain score versus placebo over the entire HZ episode (mean = 5.7 vs. 7.0, P-value = 0.032).

The burden-of-illness (BOI) score incorporates the incidence of HZ with the severity and duration of acute and chronic HZ-related pain over a 6-month period following rash onset.

The efficacy in reducing BOI was 98.4% (95% CI: 92.2; 100) in subjects  $\geq 50$  years (ZOE-50) and 92.1% (95% CI: 90.4; 93.8) in subjects  $\geq 70$  years (ZOE-50 and ZOE-70 pooled).

In Zoster-002, Shingrix significantly reduced the duration of severe ‘worst’ HZ-associated pain by 38.5% (95% CI: 11.0; 57.6) in aHSCT recipients  $\geq 18$  years with at least one confirmed HZ episode. Shingrix significantly reduced the maximum average pain score versus placebo over the entire HZ episode (mean = 4.7 vs. 5.7, P-value = 0.018) and the maximum worst pain score versus placebo over the entire HZ episode (mean = 5.8 vs. 7.1, P-value = 0.011).

The percentage of subjects with at least one confirmed HZ episode in Zoster-002 using at least one pain medication was 65.3% and 69.6% in the Shingrix and placebo group, respectively. The median duration of pain medication use was 21.5 and 47.5 days in the Shingrix and placebo group, respectively.

Additionally, in Zoster-002, the efficacy in reducing BOI score was 82.5% (95% CI: 73.6%, 91.4%).

### Long-term efficacy against HZ, PHN and HZ-related complications other than PHN

A phase IIIb, open-label, long-term follow-up study of Shingrix (Zoster-049) was conducted in adults  $\geq 50$  years from ZOE-50 and ZOE-70. Participants were enrolled approximately 5 years after they received Shingrix in ZOE-50 or ZOE-70. Adults who became immunodeficient or immunosuppressed due to disease or therapy were excluded at study entry. The TVC for efficacy included 7 408 subjects (i.e. 50.6% of 14 645 subjects included in the TVC for efficacy for studies ZOE-50 and ZOE-70). Persistence of efficacy remains unknown in immunocompromised/immunosuppressed population.

Vaccine efficacy was calculated descriptively against HZ, PHN and HZ-related complications other than PHN in the mTVC (i.e. excluding subjects who did not receive the second dose of vaccine in the primary studies, or who developed a confirmed case of HZ within one month after the second dose). Since the efficacy was estimated with regard to the first or only event, individuals who experienced a HZ, PHN, or HZ-related complication (other than PHN) during studies ZOE-50 and ZOE-70 were excluded from the corresponding efficacy analyses over the Zoster-049 duration. Estimates of incidence rates in the control group to assess the vaccine efficacy during Zoster-049 study were historical, derived from the ZOE-50 and ZOE-70 placebo groups.

Shingrix long-term efficacy results against HZ, from approximately 5 years up to approximately 11 years post-vaccination, are presented in Table 4.

**Table 4:** Long-term Shingrix efficacy against HZ (mTVC) from approximately 5 years up to approximately 11 years post-vaccination

Age at the time of vaccination (years)	Shingrix			Placebo / Historical control*			Vaccine efficacy** (%) [95% CI]
	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1 000 person years	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1 000 person years	
Over the duration of Zoster-049							
≥ 50	7 258	69	1.8	7 258	341	8.7	79.8 [73.7; 84.6]
50-59	2 043	12	1.0	2 043	90	7.7	86.7 [75.6; 93.4]
60-69	1 242	9	1.3	1 242	70	10.1	87.1 [74.2; 94.4]
≥ 70	3 973	48	2.4	3 973	179	8.8	73.2 [62.9; 80.9]

CI Confidence interval

\* Placebo group in ZOE-50 / ZOE-70 was used for Year 1 through Year 4 analysis and to form the historical control data for Year 6 and onwards analysis in Zoster-049

\*\* Descriptive efficacy analysis

Zoster-049 mTVC started at a median of 5.6 years post-vaccination in ZOE-50 / ZOE-70 and ended at a median of 11.4 years post-vaccination.

In the eleventh year after vaccination, the efficacy against HZ was 82.0% (95% CI: 63.0; 92.2) in subjects  $\geq 50$  years (Shingrix group: N=5 849), 86.7% (95% CI: 42.7; 98.5) in subjects 50-59 years (Shingrix group: N=1 883), 100.0% (95% CI: 65.1; 100.0) in subjects 60-69 years (Shingrix group: N=1 075) and 72.0% (95% CI: 33.4; 89.8) in subjects  $\geq 70$  years (Shingrix group: N=2 891).

Shingrix long-term efficacy results against PHN, from approximately 5 years up to approximately 11 years post-vaccination, are presented in Table 5.

**Table 5:** Long-term Shingrix efficacy against PHN (mTVC) from approximately 5 years up to approximately 11 years post-vaccination

Age at the time of vaccination (years)	Shingrix			Placebo / Historical control*			Vaccine efficacy*** (%) [95% CI]
	Number of evaluable subjects	Number of PHN** cases	Incidence rate per 1 000 person years	Number of evaluable subjects	Number of PHN** cases	Incidence rate per 1 000 person years	
Over the duration of Zoster-049							
≥ 50	7 271	4	0.1	7 271	32	0.8	87.5 [64.8; 96.8]
50-59	2 046	0	0.0	2 046	7	0.6	100 [46.6; 100]
60-69	1 243	1	0.1	1 243	2	0.3	50.0 [< 0; 99.2]
≥ 70	3 982	3	0.1	3 982	23	1.1	87.0 [56.8; 97.5]

CI Confidence interval

\* Placebo group in ZOE-50 / ZOE-70 was used for Year 1 through Year 4 analysis and to form the historical control data for Year 6 and onwards analysis in Zoster-049

\*\* PHN was defined as zoster-associated pain rated as ≥ 3 (on a 0-10 scale), persisting or appearing more than 90 days after onset of zoster rash using Zoster Brief Pain Inventory (ZBPI)

\*\*\* Descriptive efficacy analysis

Zoster-049 mTVC started at a median of 5.6 years post-vaccination in ZOE-50 / ZOE-70 and ended at a median of 11.4 years post-vaccination.

Shingrix efficacy against HZ-related complications other than PHN, over the duration of Zoster-049, was 91.7% (95% CI: 43.7; 99.8) and 88.9% (95% CI: 19.8; 99.8) in adults ≥ 50 years (1 vs. 12 cases) and adults ≥ 70 years (1 vs. 9 cases), respectively.

#### Subjects with a history of HZ prior to vaccination

In a phase III, randomised, placebo-controlled, observer-blind, multicentre clinical study (Zoster-062), subjects ≥ 50 years of age with a prior history of HZ (resolved > 6 months prior to enrolment) were randomised to receive 2 doses of Shingrix or placebo 2-6 months apart. There were 1 426 subjects who received at least one dose of Shingrix (N = 714) or placebo (N = 712) and 1 286 subjects completed the study with a minimum follow-up period of 26 months.

The incidence of HZ recurrence (Shingrix vs. placebo) was evaluated in the modified Exposed Set (mES; N = 1 350), including those who received two doses of Shingrix (N = 668) or placebo (N = 682) and did not have confirmed HZ within 30 days after the second dose. Data from this study do not suggest an increased risk of HZ recurrence following Shingrix vaccination in individuals with a prior history of the disease (0 HZ cases in the Shingrix group vs. 8 HZ cases in the placebo group; incidence rate ratio of HZ recurrence [Shingrix vs. placebo] 0.00 [95% CI: 0.00; 0.46]).

#### Immunogenicity of Shingrix

An immunological correlate of protection has not been established; therefore the level of immune response that provides protection against HZ is unknown.

In adults ≥ 50 years, the immune responses to Shingrix, given as 2 doses 2 months apart, were evaluated in a subset of subjects from the phase III efficacy studies ZOE-50 [humoral immunity and cell-mediated immunity (CMI)] and ZOE-70 (humoral immunity). The gE-specific immune responses (humoral and CMI) elicited by Shingrix are presented in Tables 6 and 7, respectively.

**Table 6:** Humoral immunogenicity of Shingrix in adults  $\geq 50$  years (ATP cohort for immunogenicity)

Anti-gE immune response <sup>^</sup>						
Age group (years)	Month 3*			Month 38**		
	N	GMC (mIU/mL) (95% CI)	Median fold increase of concentrations vs. pre-vaccination (Q1; Q3)	N	GMC (mIU/mL) (95% CI)	Median fold increase of concentrations vs. pre-vaccination (Q1; Q3)
ZOE-50						
$\geq 50$	1 070	52 376.6 (50 264.1; 54 577.9)	41.9 (20.8; 86.9)	967	11 919.6 (11 345.6; 12 522.7)	9.3 (4.9; 19.5)
Pooled ZOE-50 and ZOE-70						
$\geq 70$	742	49 691.5 (47 250.8; 52 258.2)	34.3 (16.7; 68.5)	648	10 507.7 (9 899.2; 11 153.6)	7.2 (3.5; 14.5)

ATP According-To-Protocol

<sup>^</sup> Anti-gE immune response = anti-gE antibody levels, measured by anti-gE enzyme-linked immunosorbent assay (gE ELISA)

\* Month 3 = 1 month post-dose 2

\*\* Month 38 = 3 years post-dose 2

N Number of evaluable subjects at the specified time point (for the GMC)

CI Confidence interval

GMC Geometric Mean Concentration

Q1; Q3 First and third quartiles

**Table 7:** Cell-mediated immunogenicity of Shingrix in adults  $\geq 50$  years (ATP cohort for immunogenicity)

gE-specific CD4[2+] T cell response <sup>^</sup>						
Age group (years)	Month 3*			Month 38**		
	N	Median frequency (Q1; Q3)	Median fold increase of frequency vs. pre-vaccination (Q1; Q3)	N	Median frequency (Q1; Q3)	Median fold increase of frequency vs. pre-vaccination (Q1; Q3)
ZOE-50						
$\geq 50$	164	1 844.1 (1 253.6; 2 932.3)	24.6 (9.9; 744.2)	152	738.9 (355.7; 1 206.5)	7.9 (2.7; 31.6)
$\geq 70^{**}$ *	52	1 494.6 (922.9; 2 067.1)	33.2 (10.0; 1 052.0)	46	480.2 (196.1; 972.4)	7.3 (1.7; 31.6)

ATP According-To-Protocol

<sup>^</sup> gE-specific CD4[2+] T cell response = gE-specific CD4+ T cell activity, measured by intracellular cytokine staining (ICS) assay (CD4[2+] T cells = CD4+ T cells expressing at least 2 of 4 selected immune markers)

\* Month 3 = 1 month post-dose 2

\*\* Month 38 = 3 years post-dose 2

N Number of evaluable subjects at the specified time point for the median frequency

Q1; Q3 First and third quartiles

\*\*\* The gE-specific CD4[2+] data in the  $\geq 70$  years of age group were only generated in ZOE-50 because CD4+ T cell activity was not assessed in ZOE-70

In IC adults  $\geq 18$  years, the humoral and CMI responses to Shingrix, given as 2 doses 1-2 months apart, were evaluated in:

- one phase I/II study: Zoster-015 (HIV infected subjects, the majority (76.42%) being stable on antiretroviral therapy (for at least one year) with a CD4 T-cell count  $\geq 200$  /mm<sup>3</sup>);
- one phase II/III study: Zoster-028 (patients with solid tumours undergoing chemotherapy);
- three phase III studies: Zoster-002 (aHSCT recipients vaccinated post-transplant), Zoster-039 (patients with hematologic malignancies vaccinated during a cancer therapy course or after the full cancer therapy course) and Zoster-041 (renal transplant recipients on chronic immunosuppressive treatment at the time of vaccination).

The gE-specific immune responses (humoral and CMI) elicited by Shingrix in all IC populations studied are presented in Tables 8 and 9, respectively.

**Table 8:** Humoral immunogenicity of Shingrix in IC adults  $\geq 18$  years (ATP cohort for immunogenicity)

Anti-gE immune response^					
	Month 3			Month 13/18/25	
N	GMC (mIU/mL) (95% CI)	Median fold increase of concentrations vs. pre-vaccination (Q1; Q3)	N	GMC (mIU/mL) (95% CI)	Median fold increase of concentrations vs. pre-vaccination (Q1; Q3)
Zoster-002 (aHSCT recipients)					
82	12 753.2 (7 973.0; 20 399.4)	14.1 (1.7; 137.0)	54	Month 13: 3 183.8 (1 869.8; 5 421.2)	Month 13: 2.7 (1.0; 24.0)
			39	Month 25: 2 819.0 (1 387.1; 5 729.1)	Month 25: 1.3 (0.6; 44.7)
Zoster-028 (solid tumour patients)					
87	18 291.7 (14 432.1; 23 183.5)	21.5 (7.0; 45.2)	68	Month 13: 4 477.3 (3 482.4; 5 756.3)	Month 13: 4.1 (2.1; 7.9)
Zoster-039 (hematologic malignancy patients)					
217	13 445.6 (10 158.9; 17 795.6)	17.2 (1.4; 87.4)	167	Month 13: 5 202.7 (4 074.8; 6 642.8)	Month 13: 5.1 (1.1; 17.0)
Zoster-041 (renal transplant recipients)					
121	19 163.8 (15 041.5; 24 416.0)	15.1 (6.1; 35.0)	111	Month 13: 8 545.1 (6 753.7; 10 811.5)	Month 13: 6.5 (3.1; 13.3)
Zoster-015 (HIV infected subjects)					
53	42 723.6 (31 233.0; 58 441.6)	40.9 (18.8; 93.0)	49	Month 18: 25 242.2 (19 618.9; 32 477.3)	Month 18: 24.0 (9.8; 39.7)

ATP According-To-Protocol

<sup>^</sup> Anti-gE immune response = anti-gE antibody levels, measured by anti-gE enzyme-linked immunosorbent assay (gE ELISA)

N Number of evaluable subjects at the specified time point (for the GMC)

CI Confidence interval

GMC Geometric Mean Concentration

Q1; Q3 First and third quartiles

In Zoster-028, GMC 1-month post Dose 2 were 22 974.3 (19 080.0; 27 663.5) in the group that received the first dose of Shingrix at least 10 days prior to a chemotherapy cycle (PreChemo group) and 9 328.0 (4 492.5; 19 368.2) in the group that received the first dose of Shingrix simultaneously with chemotherapy cycle (OnChemo group). In Zoster-039, GMC 1-month post Dose 2 were 19 934.7 (14 674.1; 27 081.2) in the group that received the first dose of Shingrix after the full cancer therapy course and 5 777.4 (3 342.5; 9 985.9) in the group that received the first dose of Shingrix during a cancer therapy course. The clinical relevance in terms of impact on efficacy, on the short and long term, is unknown.

**Table 9:** Cell-mediated immunogenicity of Shingrix in IC adults  $\geq 18$  years (ATP cohort for immunogenicity)

gE-specific CD4[2+] T cell response^					
	Month 3			Month 13/18/25	
N	Median frequency (Q1; Q3)	Median fold increase of frequency vs. pre-vaccination (Q1; Q3)	N	Median frequency (Q1; Q3)	Median fold increase of frequency vs. pre-vaccination (Q1; Q3)
Zoster-002 (aHSCT recipients)					
51	6 644.9 (1 438.3; 13 298.6)	109.0 (34.4; 2 716.4)	32	Month 13: 1,706.4 (591.4; 5 207.0)	Month 13: 43.6 (13.1; 977.8)
			30	Month 25: 2 294.4 (455.2; 3 633.2)	Month 25: 50.9 (15.3; 515.2)
Zoster-028* (solid tumour patients)					
22	778.8 (393.1; 1 098.2)	4.9 (1.7; 33.0)	18	Month 13: 332.9 (114.9; 604.6)	Month 13: 2.0 (1.3; 5.2)
Zoster-039 (hematologic malignancy patients)					
53	3 081.9 (1 766.2; 7 413.6)	45.9 (16.4; 2 221.9)	44	Month 13: 1 006.7 (416.0; 3 284.5)	Month 13: 21.4 (7.5; 351.4)
Zoster-041 (renal transplant recipients)					
32	2 149.0 (569.4; 3 695.1)	47.7 (14.7; 439.6)	33	Month 13: 1 066.3 (424.8; 1 481.5)	Month 13: 16.9 (5.9; 211.4)
Zoster-015 (HIV infected subjects)					
41	2 809.7 (1 554.5; 4 663.7)	23.4 (8.5; 604.1)	49	Month 18: 1 533.0 (770.0; 2 643.1)	Month 18: 12.0 (5.7; 507.0)

ATP According-To-Protocol

<sup>^</sup> gE-specific CD4[2+] T cell response = gE-specific CD4+ T cell activity, measured by intracellular cytokine staining (ICS) assay (CD4[2+] T cells = CD4+ T cells expressing at least 2 of 4 selected immune markers)

N Number of evaluable subjects at the specified time point for the median frequency

Q1; Q3 First and third quartiles

\* Blood for CMI was only collected from the group of subjects that received the first dose of Shingrix 8-30 days before the start of a chemotherapy cycle (i.e. largest group of the study)

#### Immunogenicity in subjects receiving 2 doses of Shingrix 6 months apart

Efficacy has not been assessed for the 0, 6-month schedule.

In a phase III, open-label clinical study (Zoster-026) where 238 adults  $\geq 50$  years of age were equally randomised to receive 2 doses of Shingrix 2 or 6 months apart, the humoral immune response following the 0, 6-month schedule was demonstrated to be non-inferior to the response with the 0, 2-month schedule. The anti-gE GMC at 1 month after the last vaccine dose was 38 153.7 mIU/mL



(95% CI: 34 205.8; 42 557.3) and 44 376.3 mIU/mL (95% CI: 39 697.0; 49 607.2) following the 0, 6-month schedule and the 0, 2-month schedule, respectively.

#### Immunogenicity in individuals previously vaccinated with live attenuated herpes zoster (HZ) vaccine

In a phase III, open-label, multicentre clinical study (Zoster-048), a 2-dose schedule of Shingrix 2 months apart was assessed in 215 adults  $\geq 65$  years of age with a previous history of vaccination with live attenuated HZ vaccine  $\geq 5$  years earlier compared to 215 matched subjects who had never received live attenuated HZ vaccine. The immune response to Shingrix was unaffected by prior vaccination with live attenuated HZ vaccine.

#### Persistence of immunogenicity

Persistence of immunogenicity was evaluated in a subset of subjects in a phase IIIb, open-label, long-term follow-up study (Zoster-049) in adults  $\geq 50$  years from ZOE-50 and ZOE-70. At Year 12 post-vaccination, the anti-gE antibody concentration in 435 evaluable subjects was 5.8-fold (95% CI: 5.2; 6.4) above pre-vaccination level (Mean Geometric Increase). Median frequency of gE specific CD4[2+] T cells at Year 12 post-vaccination in 73 evaluable subjects remained above pre-vaccination level.

Persistence of immunogenicity was evaluated in a phase IIIb, open-label study (Zoster-073) in 68 renal transplant recipients aged  $\geq 18$  years on chronic immunosuppressive therapy from Zoster-041. Zoster-073 study started 4-6 years post-vaccination in Zoster-041. At Month 24 (approximately 6-8 years post-dose 2), the anti-gE antibody concentration in 49 evaluable subjects was 2.4-fold (95% CI: 1.6; 3.7) above pre-vaccination level (Mean Geometric Increase). Median frequency of gE specific CD4[2+] T cells at Month 24 in 19 evaluable subjects in CMI subset remained above pre-vaccination level.

#### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Shingrix in one or more subsets of the paediatric population in prevention of Varicella Zoster Virus reactivation (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

Not applicable.

## **5.3 Preclinical safety data**

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

# **6. PHARMACEUTICAL PARTICULARS**

## **6.1 List of excipients**

### Powder (gE antigen)

Sucrose

Polysorbate 80 (E 433)

Sodium dihydrogen phosphate dihydrate (E 339)

Dipotassium phosphate (E 340)

### Suspension (AS01<sub>B</sub> Adjuvant System)

Diioleoyl phosphatidylcholine (E 322)  
Cholesterol  
Sodium chloride  
Disodium phosphate anhydrous (E 339)  
Potassium dihydrogen phosphate (E 340)  
Water for injections

For adjuvant see section 2.

### **6.2 Incompatibilities**

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

### **6.3 Shelf life**

42 months

#### After reconstitution

Chemical and physical in-use stability has been demonstrated for 24 hours at 30 °C.

From a microbiological point of view, the vaccine should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at 2 °C to 8 °C.

### **6.4 Special precautions for storage**

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

### **6.5 Nature and contents of container**

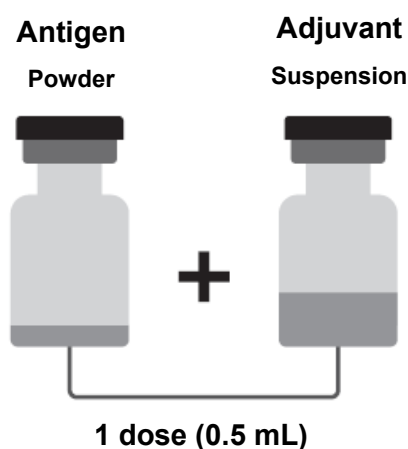
- Powder for 1 dose in a vial (type I glass) with a stopper (butyl rubber)
- Suspension for 1 dose in a vial (type I glass) with a stopper (butyl rubber).

Shingrix is available in a pack size of 1 vial of powder and 1 vial of suspension or in a pack size of 10 vials of powder and 10 vials of suspension.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

Shingrix is presented as a vial with a brown flip-off cap containing the powder (antigen) and a vial with a blue-green flip-off cap containing the suspension (adjuvant). The powder and the suspension must be reconstituted prior to administration.



The 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 syringe with a suitable needle (21G to 25G).
2. Add the entire contents of the syringe into the vial containing the powder.
3. Shake gently until the 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 – 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 the syringe.
2. Change the needle so that you are using a new needle to administer the vaccine.

### Disposal

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

## 7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals S.A.  
Rue de l'Institut 89

B-1330 Rixensart  
Belgium

**8.     MARKETING AUTHORISATION NUMBERS**

EU/1/18/1272/001  
EU/1/18/1272/002

**9.     DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 21 March 2018  
Date of latest renewal: 05 December 2022

**10.    DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

## 1. NAME OF THE MEDICINAL PRODUCT

Shingrix suspension for injection in pre-filled syringe  
Herpes zoster vaccine (recombinant, adjuvanted)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 mL) contains:

Varicella Zoster Virus<sup>1</sup> glycoprotein E antigen<sup>2,3</sup> 50 micrograms

<sup>1</sup> Varicella Zoster Virus = VZV

<sup>2</sup> adjuvanted with AS01<sub>B</sub> containing:

plant extract *Quillaja saponaria* Molina, fraction 21 (QS-21) 50 micrograms

3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* 50 micrograms

<sup>3</sup> glycoprotein E (gE) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

### Excipients with known effect

Each dose contains 0.08 milligrams of polysorbate 80 (E 433) (see section 4.4).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Suspension for injection (injection)

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

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Shingrix is indicated for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in:

- adults 50 years of age or older;
- adults 18 years of age or older at increased risk of HZ.

The use of Shingrix should be in accordance with official recommendations.

### 4.2 Posology and method of administration

#### Posology

The primary vaccination schedule consists of two doses of 0.5 mL each: an initial dose followed by a second dose 2 months later.

If flexibility in the vaccination schedule is necessary, the second dose can be administered between 2 and 6 months after the first dose (see section 5.1).

For subjects who are or might become immunodeficient or immunosuppressed due to disease or therapy, and whom would benefit from a shorter vaccination schedule, the second dose can be given 1 to 2 months after the initial dose (see section 5.1).

The need for booster doses following the primary vaccination schedule has not been established (see section 5.1).

Shingrix can be given with the same schedule in individuals previously vaccinated with live attenuated HZ vaccine (see section 5.1).

Shingrix is not indicated for prevention of primary varicella infection (chickenpox).

#### *Paediatric population*

The safety and efficacy of Shingrix in children and adolescents have not been established. No data are available.

#### Method of administration

For intramuscular injection only, preferably in the deltoid muscle.

For instructions on the handling of the vaccine before administration, see section 6.6.

### **4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

#### Prior to immunisation

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

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

The vaccine is for prophylactic use only and is not intended for treatment of established clinical disease.

Shingrix should not be administered intravascularly or intradermally.

Subcutaneous administration is not recommended.

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

Shingrix should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following intramuscular administration to these subjects.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

There are no safety, immunogenicity or efficacy data to support replacing a dose of Shingrix with a dose of another HZ vaccine.

#### Excipients with known effect

##### *Polysorbate 80*

This medicinal product contains 0.08 mg of polysorbate 80 per dose. Polysorbates may cause allergic reactions.

##### *Sodium*

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

##### *Potassium*

This medicinal product contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially 'potassium-free'.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Shingrix can be given concomitantly with seasonal influenza vaccine (inactivated, unadjuvanted), 23-valent pneumococcal polysaccharide vaccine (PPV23), 13-valent pneumococcal conjugate vaccine (PCV13), reduced antigen diphtheria-tetanus-acellular pertussis vaccine (dTpa), coronavirus disease 2019 (COVID-19) messenger ribonucleic acid (mRNA) vaccine or respiratory syncytial virus (RSV) vaccine (recombinant, adjuvanted). The vaccines should be administered at different injection sites.

The adverse reactions of fever and shivering were more frequent when PPV23 vaccine was co-administered with Shingrix (16% and 21%, respectively) compared to when Shingrix was given alone (7% for both adverse reactions).

In adults aged 50 years and above, systemic adverse reactions that are very commonly reported (see Table 1; such as myalgia 32.9%, fatigue 32.2%, and headache 26.3%), and arthralgia, uncommonly reported, following administration of Shingrix alone were reported with increased frequency when Shingrix was co-administered with a COVID-19 mRNA vaccine (myalgia 64%, fatigue 51.7%, headache 39%, arthralgia 30.3%).

Concomitant administration of Shingrix with other vaccines than those listed above has not been studied.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

There are no data from the use of Shingrix in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Shingrix during pregnancy.

##### Breast-feeding

The effect on breast-fed infants of administration of Shingrix to their mothers has not been studied. It is unknown whether Shingrix is excreted in human milk.

##### Fertility

Animal studies do not indicate direct or indirect effects with respect to fertility in males or females (see section 5.3).

#### **4.7 Effects on ability to drive and use machines**

Shingrix may have a minor influence on the ability to drive and use machines in the 2-3 days following vaccination. Fatigue and malaise may occur following administration (see section 4.8).

#### **4.8 Undesirable effects**

##### Summary of the safety profile

In adults aged 50 years and above, the most frequently reported adverse reactions were pain at the injection site (68.1% overall/dose; 3.8% severe/dose), myalgia (32.9% overall/dose; 2.9% severe/dose), fatigue (32.2% overall/dose; 3.0% severe/dose) and headache (26.3% overall/dose; 1.9% severe/dose). Most of these reactions were not long-lasting (median duration of 2 to 3 days). Reactions reported as severe lasted 1 to 2 days.

In adults  $\geq 18$  years of age who are immunodeficient or immunosuppressed due to disease or therapy (referred to as immunocompromised (IC)), the safety profile was consistent with that observed in adults 50 years and above. There are limited data in adults aged 18-49 years at increased risk of HZ who are not IC.

Overall, there was a higher incidence of some adverse reactions in younger age groups:

- studies in IC adults  $\geq 18$  years of age (pooled analysis): the incidence of pain at the injection site, fatigue, myalgia, headache, shivering and fever was higher in adults aged 18-49 years compared to those aged 50 years and above.
- studies in adults  $\geq 50$  years of age (pooled analysis): the incidence of myalgia, fatigue, headache, shivering, fever and gastrointestinal symptoms was higher in adults aged 50-69 years compared to those aged 70 years and above.

##### Tabulated list of adverse reactions

The safety profile presented below is based on a pooled analysis of data generated in placebo-controlled clinical studies on 5 887 adults 50-69 years of age and 8 758 adults  $\geq 70$  years of age. Of these 14 645 adults, 7 408 were included in a long-term follow-up extension study over a follow-up period of approximately 11 years after vaccination.

In clinical studies in IC adults  $\geq 18$  years of age (1 587 subjects) the safety profile is consistent with the data presented in Table 1 below.

Adverse reactions reported during post-marketing surveillance are also tabulated below.

Adverse reactions reported are listed according to the following frequency:

Very common	( $\geq 1/10$ )
Common	( $\geq 1/100$ to $< 1/10$ )
Uncommon	( $\geq 1/1\ 000$ to $< 1/100$ )
Rare	( $\geq 1/10\ 000$ to $< 1/1\ 000$ )
Very rare	( $< 1/10\ 000$ )

Within each frequency grouping the adverse reactions are reported in the order of decreasing seriousness.



**Table 1:** Adverse reactions

System Organ Class <sup>1</sup>	Frequency	Adverse reactions
Blood and lymphatic system disorders	Uncommon	lymphadenopathy
Immune system disorders	Rare	hypersensitivity reactions including rash, urticaria, angioedema <sup>2</sup>
Nervous system disorders	Very common	headache
	Very rare	Guillain-Barré syndrome <sup>3</sup>
Gastrointestinal disorders	Very common	gastrointestinal symptoms (including nausea, vomiting, diarrhoea and/or abdominal pain)
Musculoskeletal and connective tissue disorders	Very common	myalgia
	Uncommon	arthralgia
General disorders and administration site conditions	Very common	injection site reactions (such as pain, redness, swelling), fatigue, chills, fever
	Common	injection site pruritus, malaise

<sup>1</sup>According to MedDRA (medical dictionary for regulatory activities) terminology

<sup>2</sup>Adverse reactions from spontaneous reporting

<sup>3</sup> See ‘Description of selected adverse reactions’

#### Description of selected adverse reactions

##### *Post-marketing observational studies of the risk of Guillain-Barré syndrome*

In 2 similar post-marketing observational studies in the US among individuals aged 65 years or older, an increased risk of Guillain-Barré syndrome (estimated 3 to 7 excess cases per million doses administered) was observed during the 42 days following any dose of Shingrix. In further analyses, the increased risk was observed following the first dose of Shingrix (estimated 6 to 12 excess cases of Guillain-Barré syndrome per million doses administered), but no increased risk was observed following the second dose.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

## **4.9 Overdose**

No case of overdose has been reported.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Vaccines, varicella zoster vaccines, ATC code: J07BK03.

### Mechanism of action

By combining the VZV specific antigen (gE) with an adjuvant system (AS01<sub>B</sub>), Shingrix is designed to induce antigen-specific cellular and humoral immune responses in individuals with pre-existing immunity against VZV.

Non-clinical data show that AS01<sub>B</sub> induces a local and transient activation of the innate immune system through specific molecular pathways. 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<sup>+</sup> T cells and antibodies. The adjuvant effect of AS01<sub>B</sub> is the result of interactions between MPL and QS-21 formulated in liposomes.

### Clinical efficacy of Shingrix

#### Efficacy against Herpes Zoster (HZ) and Post-Herpetic Neuralgia (PHN)

Two phase III, placebo-controlled, observer-blind efficacy studies of Shingrix were conducted in adults  $\geq 50$  years with 2 doses administered 2 months apart:

- ZOE-50 (Zoster-006): Total Vaccinated Cohort (TVC) of 15 405 adults  $\geq 50$  years who received at least one dose of either Shingrix (N=7 695) or placebo (N=7 710).
- ZOE-70 (Zoster-022): TVC of 13 900 adults  $\geq 70$  years who received at least one dose of either Shingrix (N=6 950) or placebo (N=6 950).

The studies were not designed to demonstrate efficacy in subgroups of frail individuals, including those with multiple comorbidities, although these subjects were not excluded from the studies.

Two phase III, placebo-controlled, observer-blind studies evaluating Shingrix efficacy were conducted in IC adults  $\geq 18$  years with 2 doses administered 1-2 months apart:

- Zoster-002: TVC of 1 846 autologous hematopoietic stem cell transplants (aHSCT) recipients who received at least one dose of either Shingrix (N=922) or placebo (N=924) 50-70 days post-transplant, 21.3% (Shingrix) and 20.5% (placebo) of the subjects received at least one immunosuppressive (IS) treatment (for a duration of at least one day) from HSCT up to 30 days after Dose 2 (TVC). The proportion of subjects by underlying disease was: 53.1% (Shingrix) and 53.4% (placebo) for multiple myeloma (MM) and 46.9% (Shingrix) and 46.6% (placebo) for other diagnosis.
- Zoster-039: TVC of 562 subjects with hematologic malignancies who received at least one dose of either Shingrix (N=283) or placebo (N=279) during a cancer therapy course (37%) or after the full cancer therapy course (63%). The proportion of subjects by underlying disease was: 70.7% (Shingrix) and 71.3% (placebo) for MM and other diseases, 14.5% (Shingrix) and 14.0% (placebo) for non-Hodgkin B-cell lymphoma (NHBCL) and 14.8% (Shingrix) and 14.7% (placebo) for chronic lymphocytic leukaemia (CLL).

These studies were not designed to assess the impact of concomitant use of IS therapy on vaccine efficacy or to assess the impact of specific IS treatments on vaccine efficacy. Most vaccine recipients were not under IS therapy at the time of vaccination (see above). Not all types of IS therapies were used in the populations studied.

Incidence of HZ and PHN cases as well as vaccine efficacy were evaluated in the modified Total Vaccinated Cohort (mTVC), i.e. excluding adults who did not receive the second dose of vaccine or who had a confirmed diagnosis of HZ within one month after the second dose.

Shingrix significantly decreased the incidence of HZ compared with placebo in:

- adults  $\geq 50$  years (ZOE-50): 6 vs. 210 cases;
- adults  $\geq 70$  years (pooled analysis of ZOE-50 and ZOE-70): 25 vs. 284 cases;
- adults  $\geq 18$  years with aHSCT (Zoster-002): 49 vs. 135 cases;
- adults  $\geq 18$  years with hematologic malignancies (Zoster-039): 2 vs. 14 cases. Vaccine efficacy was calculated post-hoc.

Vaccine efficacy results against HZ are presented in Table 2.

**Table 2:** Shingrix efficacy against HZ (mTVC)

Age (years)	Shingrix			Placebo			Vaccine efficacy (%) [95% CI]
	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1 000 person years	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1 000 person years	
ZOE-50*							
≥ 50	7 344	6	0.3	7 415	210	9.1	97.2 [93.7; 99.0]
50-59	3 492	3	0.3	3 525	87	7.8	96.6 [89.6; 99.4]
≥ 60	3 852	3	0.2	3 890	123	10.2	97.6 [92.7; 99.6]
60-69	2 141	2	0.3	2 166	75	10.8	97.4 [90.1; 99.7]
Pooled ZOE-50 and ZOE-70**							
≥ 70	8 250	25	0.8	8 346	284	9.3	91.3 [86.8; 94.5]
70-79	6 468	19	0.8	6 554	216	8.9	91.3 [86.0; 94.9]
≥ 80	1 782	6	1.0	1 792	68	11.1	91.4 [80.2; 97.0]
Zoster-002*** (aHSCT recipients <sup>#</sup> )							
≥ 18	870	49	30.0	851	135	94.3	68.2 [55.5; 77.6]
18-49	213	9	21.5	212	29	76.0	71.8 [38.7; 88.3]
≥ 50	657	40	33.0	639	106	100.9	67.3 [52.6; 77.9]
Zoster-039 (hematologic malignancy patients <sup>#</sup> )							
≥ 18	259	2	8.5	256	14	66.2	87.2**** [44.2; 98.6]

CI Confidence interval

\* Over a median follow-up period of 3.1 years

\*\* Over a median follow-up period of 4.0 years

Data in subjects ≥ 70 years of age are sourced from the pre-specified pooled analyses of ZOE-50 and ZOE-70 (mTVC) as these analyses provide the most robust estimates for vaccine efficacy in this age group.

\*\*\* Over a median follow-up period of 21 months

\*\*\*\* VE calculation was performed post-hoc; median follow-up period of 11.1 months

# antiviral prophylaxis in line with the local standard of care was permitted

Approximately 13 000 subjects with underlying medical conditions, including conditions associated with a higher risk of HZ, were enrolled in ZOE-50 and ZOE-70. Post-hoc analysis of efficacy against confirmed HZ undertaken in patients with common conditions (chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, depression or diabetes mellitus), indicates that the vaccine efficacy is aligned with the overall HZ efficacy.

Shingrix significantly decreased the incidence of PHN compared with placebo in:

- adults ≥ 50 years (ZOE-50): 0 vs. 18 cases;

- adults  $\geq 70$  years (pooled analysis of ZOE-50 and ZOE-70): 4 vs. 36 cases;
- adults  $\geq 18$  years with aHSCT (Zoster-002): 1 vs. 9 cases.

Vaccine efficacy results against PHN are presented in Table 3.

**Table 3:** Shingrix efficacy against PHN (mTVC)

Age (years)	Shingrix			Placebo			Vaccine efficacy (%) [95% CI]
	Number of evaluable subjects	Number of PHN* cases	Incidence rate per 1 000 person years	Number of evaluable subjects	Number of PHN* cases	Incidence rate per 1 000 person years	
ZOE-50**							
≥ 50	7 340	0	0.0	7 413	18	0.6	100 [77.1; 100]
50-59	3 491	0	0.0	3 523	8	0.6	100 [40.8; 100]
≥ 60	3 849	0	0.0	3 890	10	0.7	100 [55.2; 100]
60-69	2 140	0	0.0	2 166	2	0.2	100 <sup>§</sup> [< 0; 100]
Pooled ZOE-50 and ZOE-70***							
≥ 70	8 250	4	0.1	8 346	36	1.2	88.8 [68.7; 97.1]
70-79	6 468	2	0.1	6 554	29	1.2	93.0 [72.4; 99.2]
≥ 80	1 782	2	0.3	1 792	7	1.1	71.2 <sup>§</sup> [< 0; 97.1]
Zoster-002**** (aHSCT recipients <sup>#</sup> )							
≥ 18	870	1	0.5	851	9	4.9	89.3 [22.5; 99.8]
18-49	213	0	0.0	212	1	2.2	100.0 <sup>§</sup> [< 0; 100.0]
≥ 50	657	1	0.7	639	8	5.8	88.0 [10.4; 99.8]

\* PHN was defined as zoster-associated pain rated as  $\geq 3$  (on a 0-10 scale), persisting or appearing more than 90 days after onset of zoster rash using Zoster Brief Pain Inventory (ZBPI)

CI Confidence interval

\*\* Over a median follow-up period of 4.1 years

\*\*\* Over a median follow-up period of 4.0 years

Data in subjects  $\geq 70$  years of age are sourced from the pre-specified pooled analyses of ZOE-50 and ZOE-70 (mTVC) as these analyses provide the most robust estimates for vaccine efficacy in this age group.

\*\*\*\* Over a median follow-up period of 21 months

§ Not statistically significant

# antiviral prophylaxis in line with the local standard of care was permitted

The benefit of Shingrix in the prevention of 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.

In the fourth year after vaccination, the efficacy against HZ was 93.1% (95% CI: 81.2; 98.2) and 87.9% (95% CI: 73.3; 95.4) in adults  $\geq 50$  years (ZOE-50) and adults  $\geq 70$  years (pooled ZOE-50 and ZOE-70), respectively.

In Zoster-002, during a follow-up period starting 1 month post-dose 2 (i.e. corresponding to approximately 6 months after aHSCT) until 1 year after aHSCT, when the risk for HZ is the highest, the efficacy against HZ was 76.2% (95% CI: 61.1; 86.0).

#### Efficacy against HZ-related complications other than PHN

The evaluated HZ-related complications (other than PHN) were: HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease including stroke, and visceral disease. In the pooled analysis of ZOE-50 and ZOE-70, Shingrix significantly reduced these HZ-related complications by 93.7% (95% CI: 59.5; 99.9) and 91.6% (95% CI: 43.3; 99.8) in adults  $\geq 50$  years (1 vs. 16 cases) and adults  $\geq 70$  years (1 vs. 12 cases), respectively. No cases of visceral disease or stroke were reported during these studies.

In Zoster-002, Shingrix significantly reduced HZ-related complications by 77.8% (95% CI: 19.0; 96.0) in aHSCT recipients  $\geq 18$  years (3 vs. 13 cases).

In addition, in Zoster-002, Shingrix significantly reduced HZ-related hospitalisations by 84.7% (95% CI: 32.1; 96.6) (2 vs. 13 cases).

#### Effect of Shingrix on HZ-related pain

Overall in ZOE-50 and ZOE-70, there was a general trend towards less severe HZ-related pain in subjects vaccinated with Shingrix compared to placebo. As a consequence of the high vaccine efficacy against HZ, a low number of breakthrough cases were accrued, and it was therefore not possible to draw firm conclusions on these study objectives.

In subjects  $\geq 70$  years with at least one confirmed HZ episode (ZOE-50 and ZOE-70 pooled), Shingrix significantly reduced the use and the duration of HZ-related pain medication by 39.0% (95% CI: 11.9; 63.3) and 50.6% (95% CI: 8.8; 73.2), respectively. The median duration of pain medication use was 32.0 and 44.0 days in the Shingrix and placebo group, respectively.

In subjects with at least one confirmed HZ episode, Shingrix significantly reduced the maximum average pain score versus placebo over the entire HZ episode (mean = 3.9 vs. 5.5, P-value = 0.049 and mean = 4.5 vs. 5.6, P-value = 0.043, in subjects  $\geq 50$  years (ZOE-50) and  $\geq 70$  years (ZOE-50 and ZOE-70 pooled), respectively). In addition, in subjects  $\geq 70$  years (ZOE-50 and ZOE-70 pooled), Shingrix significantly reduced the maximum worst pain score versus placebo over the entire HZ episode (mean = 5.7 vs. 7.0, P-value = 0.032).

The burden-of-illness (BOI) score incorporates the incidence of HZ with the severity and duration of acute and chronic HZ-related pain over a 6-month period following rash onset.

The efficacy in reducing BOI was 98.4% (95% CI: 92.2; 100) in subjects  $\geq 50$  years (ZOE-50) and 92.1% (95% CI: 90.4; 93.8) in subjects  $\geq 70$  years (ZOE-50 and ZOE-70 pooled).

In Zoster-002, Shingrix significantly reduced the duration of severe ‘worst’ HZ-associated pain by 38.5% (95% CI: 11.0; 57.6) in aHSCT recipients  $\geq 18$  years with at least one confirmed HZ episode. Shingrix significantly reduced the maximum average pain score versus placebo over the entire HZ episode (mean = 4.7 vs. 5.7, P-value = 0.018) and the maximum worst pain score versus placebo over the entire HZ episode (mean = 5.8 vs. 7.1, P-value = 0.011).

The percentage of subjects with at least one confirmed HZ episode in Zoster-002 using at least one pain medication was 65.3% and 69.6% in the Shingrix and placebo group, respectively. The median duration of pain medication use was 21.5 and 47.5 days in the Shingrix and placebo group, respectively.

Additionally, in Zoster-002, the efficacy in reducing BOI score was 82.5% (95% CI: 73.6%, 91.4%).

### Long-term efficacy against HZ, PHN and HZ-related complications other than PHN

A phase IIIb, open-label, long-term follow-up study of Shingrix (Zoster-049) was conducted in adults  $\geq 50$  years from ZOE-50 and ZOE-70. Participants were enrolled approximately 5 years after they received Shingrix in ZOE-50 or ZOE-70. Adults who became immunodeficient or immunosuppressed due to disease or therapy were excluded at study entry. The TVC for efficacy included 7 408 subjects (i.e. 50.6% of 14 645 subjects included in the TVC for efficacy for studies ZOE-50 and ZOE-70). Persistence of efficacy remains unknown in immunocompromised/immunosuppressed population.

Vaccine efficacy was calculated descriptively against HZ, PHN and HZ-related complications other than PHN in the mTVC (i.e. excluding subjects who did not receive the second dose of vaccine in the primary studies, or who developed a confirmed case of HZ within one month after the second dose). Since the efficacy was estimated with regard to the first or only event, individuals who experienced a HZ, PHN, or HZ-related complication (other than PHN) during studies ZOE-50 and ZOE-70 were excluded from the corresponding efficacy analyses over the Zoster-049 duration. Estimates of incidence rates in the control group to assess the vaccine efficacy during Zoster-049 study were historical, derived from the ZOE-50 and ZOE-70 placebo groups.

Shingrix long-term efficacy results against HZ, from approximately 5 years up to approximately 11 years post-vaccination, are presented in Table 4.

**Table 4:** Long-term Shingrix efficacy against HZ (mTVC) from approximately 5 years up to approximately 11 years post-vaccination

Age at the time of vaccination (years)	Shingrix			Placebo / Historical control*			Vaccine efficacy** (%) [95% CI]
	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1 000 person years	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1 000 person years	
Over the duration of Zoster-049							
≥ 50	7 258	69	1.8	7 258	341	8.7	79.8 [73.7; 84.6]
50-59	2 043	12	1.0	2 043	90	7.7	86.7 [75.6; 93.4]
60-69	1 242	9	1.3	1 242	70	10.1	87.1 [74.2; 94.4]
≥ 70	3 973	48	2.4	3 973	179	8.8	73.2 [62.9; 80.9]

CI Confidence interval

\* Placebo group in ZOE-50 / ZOE-70 was used for Year 1 through Year 4 analysis and to form the historical control data for Year 6 and onwards analysis in Zoster-049

\*\* Descriptive efficacy analysis

Zoster-049 mTVC started at a median of 5.6 years post-vaccination in ZOE-50 / ZOE-70 and ended at a median of 11.4 years post-vaccination.

In the eleventh year after vaccination, the efficacy against HZ was 82.0% (95% CI: 63.0; 92.2) in subjects  $\geq 50$  years (Shingrix group: N=5 849), 86.7% (95% CI: 42.7; 98.5) in subjects 50-59 years (Shingrix group: N=1 883), 100.0% (95% CI: 65.1; 100.0) in subjects 60-69 years (Shingrix group: N=1 075) and 72.0% (95% CI: 33.4; 89.8) in subjects  $\geq 70$  years (Shingrix group: N=2 891).

Shingrix long-term efficacy results against PHN, from approximately 5 years up to approximately 11 years post-vaccination, are presented in Table 5.

**Table 5:** Long-term Shingrix efficacy against PHN (mTVC) from approximately 5 years up to approximately 11 years post-vaccination

Age at the time of vaccination (years)	Shingrix			Placebo / Historical control*			Vaccine efficacy*** (%) [95% CI]
	Number of evaluable subjects	Number of PHN** cases	Incidence rate per 1 000 person years	Number of evaluable subjects	Number of PHN** cases	Incidence rate per 1 000 person years	
Over the duration of Zoster-049							
≥ 50	7 271	4	0.1	7 271	32	0.8	87.5 [64.8; 96.8]
50-59	2 046	0	0.0	2 046	7	0.6	100 [46.6; 100]
60-69	1 243	1	0.1	1 243	2	0.3	50.0 [< 0; 99.2]
≥ 70	3 982	3	0.1	3 982	23	1.1	87.0 [56.8; 97.5]

CI Confidence interval

\* Placebo group in ZOE-50 / ZOE-70 was used for Year 1 through Year 4 analysis and to form the historical control data for Year 6 and onwards analysis in Zoster-049

\*\* PHN was defined as zoster-associated pain rated as  $\geq 3$  (on a 0-10 scale), persisting or appearing more than 90 days after onset of zoster rash using Zoster Brief Pain Inventory (ZBPI)

\*\*\* Descriptive efficacy analysis

Zoster-049 mTVC started at a median of 5.6 years post-vaccination in ZOE-50 / ZOE-70 and ended at a median of 11.4 years post-vaccination.

Shingrix efficacy against HZ-related complications other than PHN, over the duration of Zoster-049, was 91.7% (95% CI: 43.7; 99.8) and 88.9% (95% CI: 19.8; 99.8) in adults  $\geq 50$  years (1 vs. 12 cases) and adults  $\geq 70$  years (1 vs. 9 cases), respectively.

#### Subjects with a history of HZ prior to vaccination

In a phase III, randomised, placebo-controlled, observer-blind, multicentre clinical study (Zoster-062), subjects  $\geq 50$  years of age with a prior history of HZ (resolved  $> 6$  months prior to enrolment) were randomised to receive 2 doses of Shingrix or placebo 2-6 months apart. There were 1 426 subjects who received at least one dose of Shingrix (N = 714) or placebo (N = 712) and 1 286 subjects completed the study with a minimum follow-up period of 26 months.

The incidence of HZ recurrence (Shingrix vs. placebo) was evaluated in the modified Exposed Set (mES; N = 1 350), including those who received two doses of Shingrix (N = 668) or placebo (N = 682) and did not have confirmed HZ within 30 days after the second dose. Data from this study do not suggest an increased risk of HZ recurrence following Shingrix vaccination in individuals with a prior history of the disease (0 HZ cases in the Shingrix group vs. 8 HZ cases in the placebo group; incidence rate ratio of HZ recurrence [Shingrix vs. placebo] 0.00 [95% CI: 0.00; 0.46]).

#### Immunogenicity of Shingrix

An immunological correlate of protection has not been established; therefore the level of immune response that provides protection against HZ is unknown.

In adults  $\geq 50$  years, the immune responses to Shingrix, given as 2 doses 2 months apart, were evaluated in a subset of subjects from the phase III efficacy studies ZOE-50 [humoral immunity and cell-mediated immunity (CMI)] and ZOE-70 (humoral immunity). The gE-specific immune responses (humoral and CMI) elicited by Shingrix are presented in Tables 6 and 7, respectively.

**Table 6:** Humoral immunogenicity of Shingrix in adults  $\geq 50$  years (ATP cohort for immunogenicity)

Anti-gE immune response <sup>^</sup>						
Age group (years)	Month 3*			Month 38**		
	N	GMC (mIU/mL) (95% CI)	Median fold increase of concentrations vs. pre-vaccination (Q1; Q3)	N	GMC (mIU/mL) (95% CI)	Median fold increase of concentrations vs. pre-vaccination (Q1; Q3)
ZOE-50						
$\geq 50$	1 070	52 376.6 (50 264.1; 54 577.9)	41.9 (20.8; 86.9)	967	11 919.6 (11 345.6; 12 522.7)	9.3 (4.9; 19.5)
Pooled ZOE-50 and ZOE-70						
$\geq 70$	742	49 691.5 (47 250.8; 52 258.2)	34.3 (16.7; 68.5)	648	10 507.7 (9 899.2; 11 153.6)	7.2 (3.5; 14.5)

ATP According-To-Protocol

<sup>^</sup> Anti-gE immune response = anti-gE antibody levels, measured by anti-gE enzyme-linked immunosorbent assay (gE ELISA)

\* Month 3 = 1 month post-dose 2

\*\* Month 38 = 3 years post-dose 2

N Number of evaluable subjects at the specified time point (for the GMC)

CI Confidence interval

GMC Geometric Mean Concentration

Q1; Q3 First and third quartiles



**Table 7:** Cell-mediated immunogenicity of Shingrix in adults  $\geq 50$  years (ATP cohort for immunogenicity)

gE-specific CD4[2+] T cell response <sup>^</sup>						
Age group (years)	Month 3*			Month 38**		
	N	Median frequency (Q1; Q3)	Median fold increase of frequency vs. pre-vaccination (Q1; Q3)	N	Median frequency (Q1; Q3)	Median fold increase of frequency vs. pre-vaccination (Q1; Q3)
ZOE-50						
$\geq 50$	164	1 844.1 (1 253.6; 2 932.3)	24.6 (9.9; 744.2)	152	738.9 (355.7; 1 206.5)	7.9 (2.7; 31.6)
$\geq 70^{**}$ *	52	1 494.6 (922.9; 2 067.1)	33.2 (10.0; 1 052.0)	46	480.2 (196.1; 972.4)	7.3 (1.7; 31.6)

ATP According-To-Protocol

<sup>^</sup> gE-specific CD4[2+] T cell response = gE-specific CD4+ T cell activity, measured by intracellular cytokine staining (ICS) assay (CD4[2+] T cells = CD4+ T cells expressing at least 2 of 4 selected immune markers)

\* Month 3 = 1 month post-dose 2

\*\* Month 38 = 3 years post-dose 2

N Number of evaluable subjects at the specified time point for the median frequency

Q1; Q3 First and third quartiles

\*\*\* The gE-specific CD4[2+] data in the  $\geq 70$  years of age group were only generated in ZOE-50 because CD4+ T cell activity was not assessed in ZOE-70

In IC adults  $\geq 18$  years, the humoral and CMI responses to Shingrix, given as 2 doses 1-2 months apart, were evaluated in:

- one phase I/II study: Zoster-015 (HIV infected subjects, the majority (76.42%) being stable on antiretroviral therapy (for at least one year) with a CD4 T-cell count  $\geq 200$  /mm<sup>3</sup>);
- one phase II/III study: Zoster-028 (patients with solid tumours undergoing chemotherapy);
- three phase III studies: Zoster-002 (aHSCT recipients vaccinated post-transplant), Zoster-039 (patients with hematologic malignancies vaccinated during a cancer therapy course or after the full cancer therapy course) and Zoster-041 (renal transplant recipients on chronic immunosuppressive treatment at the time of vaccination).

The gE-specific immune responses (humoral and CMI) elicited by Shingrix in all IC populations studied are presented in Tables 8 and 9, respectively.

**Table 8:** Humoral immunogenicity of Shingrix in IC adults  $\geq 18$  years (ATP cohort for immunogenicity)

Anti-gE immune response^					
	Month 3			Month 13/18/25	
N	GMC (mIU/mL) (95% CI)	Median fold increase of concentrations vs. pre-vaccination (Q1; Q3)	N	GMC (mIU/mL) (95% CI)	Median fold increase of concentrations vs. pre-vaccination (Q1; Q3)
Zoster-002 (aHSCT recipients)					
82	12 753.2 (7 973.0; 20 399.4)	14.1 (1.7; 137.0)	54	Month 13: 3 183.8 (1 869.8; 5 421.2)	Month 13: 2.7 (1.0; 24.0)
			39	Month 25: 2 819.0 (1 387.1; 5 729.1)	Month 25: 1.3 (0.6; 44.7)
Zoster-028 (solid tumour patients)					
87	18 291.7 (14 432.1; 23 183.5)	21.5 (7.0; 45.2)	68	Month 13: 4 477.3 (3 482.4; 5 756.3)	Month 13: 4.1 (2.1; 7.9)
Zoster-039 (hematologic malignancy patients)					
217	13 445.6 (10 158.9; 17 795.6)	17.2 (1.4; 87.4)	167	Month 13: 5 202.7 (4 074.8; 6 642.8)	Month 13: 5.1 (1.1; 17.0)
Zoster-041 (renal transplant recipients)					
121	19 163.8 (15 041.5; 24 416.0)	15.1 (6.1; 35.0)	111	Month 13: 8 545.1 (6 753.7; 10 811.5)	Month 13: 6.5 (3.1; 13.3)
Zoster-015 (HIV infected subjects)					
53	42 723.6 (31 233.0; 58 441.6)	40.9 (18.8; 93.0)	49	Month 18: 25 242.2 (19 618.9; 32 477.3)	Month 18: 24.0 (9.8; 39.7)

ATP According-To-Protocol

<sup>^</sup> Anti-gE immune response = anti-gE antibody levels, measured by anti-gE enzyme-linked immunosorbent assay (gE ELISA)

N Number of evaluable subjects at the specified time point (for the GMC)

CI Confidence interval

GMC Geometric Mean Concentration

Q1; Q3 First and third quartiles

In Zoster-028, GMC 1-month post Dose 2 were 22 974.3 (19 080.0; 27 663.5) in the group that received the first dose of Shingrix at least 10 days prior to a chemotherapy cycle (PreChemo group) and 9 328.0 (4 492.5; 19 368.2) in the group that received the first dose of Shingrix simultaneously with chemotherapy cycle (OnChemo group). In Zoster-039, GMC 1-month post Dose 2 were 19 934.7 (14 674.1; 27 081.2) in the group that received the first dose of Shingrix after the full cancer therapy course and 5 777.4 (3 342.5; 9 985.9) in the group that received the first dose of Shingrix during a cancer therapy course. The clinical relevance in terms of impact on efficacy, on the short and long term, is unknown.

**Table 9:** Cell-mediated immunogenicity of Shingrix in IC adults  $\geq 18$  years (ATP cohort for immunogenicity)

gE-specific CD4[2+] T cell response^					
	Month 3			Month 13/18/25	
N	Median frequency (Q1; Q3)	Median fold increase of frequency vs. pre-vaccination (Q1; Q3)	N	Median frequency (Q1; Q3)	Median fold increase of frequency vs. pre-vaccination (Q1; Q3)
Zoster-002 (aHSCT recipients)					
51	6 644.9 (1 438.3; 13 298.6)	109.0 (34.4; 2 716.4)	32	Month 13: 1,706.4 (591.4; 5 207.0)	Month 13: 43.6 (13.1; 977.8)
			30	Month 25: 2 294.4 (455.2; 3 633.2)	Month 25: 50.9 (15.3; 515.2)
Zoster-028* (solid tumour patients)					
22	778.8 (393.1; 1 098.2)	4.9 (1.7; 33.0)	18	Month 13: 332.9 (114.9; 604.6)	Month 13: 2.0 (1.3; 5.2)
Zoster-039 (hematologic malignancy patients)					
53	3 081.9 (1 766.2; 7 413.6)	45.9 (16.4; 2 221.9)	44	Month 13: 1 006.7 (416.0; 3 284.5)	Month 13: 21.4 (7.5; 351.4)
Zoster-041 (renal transplant recipients)					
32	2 149.0 (569.4; 3 695.1)	47.7 (14.7; 439.6)	33	Month 13: 1 066.3 (424.8; 1 481.5)	Month 13: 16.9 (5.9; 211.4)
Zoster-015 (HIV infected subjects)					
41	2 809.7 (1 554.5; 4 663.7)	23.4 (8.5; 604.1)	49	Month 18: 1 533.0 (770.0; 2 643.1)	Month 18: 12.0 (5.7; 507.0)

ATP According-To-Protocol

<sup>^</sup> gE-specific CD4[2+] T cell response = gE-specific CD4+ T cell activity, measured by intracellular cytokine staining (ICS) assay (CD4[2+] T cells = CD4+ T cells expressing at least 2 of 4 selected immune markers)

N Number of evaluable subjects at the specified time point for the median frequency

Q1; Q3 First and third quartiles

\* Blood for CMI was only collected from the group of subjects that received the first dose of Shingrix 8-30 days before the start of a chemotherapy cycle (i.e. largest group of the study)

#### Immunogenicity in subjects receiving 2 doses of Shingrix 6 months apart

Efficacy has not been assessed for the 0, 6-month schedule.

In a phase III, open-label clinical study (Zoster-026) where 238 adults  $\geq 50$  years of age were equally randomised to receive 2 doses of Shingrix 2 or 6 months apart, the humoral immune response following the 0, 6-month schedule was demonstrated to be non-inferior to the response with the 0, 2-month schedule. The anti-gE GMC at 1 month after the last vaccine dose was 38 153.7 mIU/mL

(95% CI: 34 205.8; 42 557.3) and 44 376.3 mIU/mL (95% CI: 39 697.0; 49 607.2) following the 0, 6-month schedule and the 0, 2-month schedule, respectively.

#### Immunogenicity in individuals previously vaccinated with live attenuated herpes zoster (HZ) vaccine

In a phase III, open-label, multicentre clinical study (Zoster-048), a 2-dose schedule of Shingrix 2 months apart was assessed in 215 adults  $\geq 65$  years of age with a previous history of vaccination with live attenuated HZ vaccine  $\geq 5$  years earlier compared to 215 matched subjects who had never received live attenuated HZ vaccine. The immune response to Shingrix was unaffected by prior vaccination with live attenuated HZ vaccine.

#### Persistence of immunogenicity

Persistence of immunogenicity was evaluated in a subset of subjects in a phase IIIb, open-label, long-term follow-up study (Zoster-049) in adults  $\geq 50$  years from ZOE-50 and ZOE-70. At Year 12 post-vaccination, the anti-gE antibody concentration in 435 evaluable subjects was 5.8-fold (95% CI: 5.2; 6.4) above pre-vaccination level (Mean Geometric Increase). Median frequency of gE specific CD4[2+] T cells at Year 12 post-vaccination in 73 evaluable subjects remained above pre-vaccination level.

Persistence of immunogenicity was evaluated in a phase IIIb, open-label study (Zoster-073) in 68 renal transplant recipients aged  $\geq 18$  years on chronic immunosuppressive therapy from Zoster-041. Zoster-073 study started 4-6 years post-vaccination in Zoster-041. At Month 24 (approximately 6-8 years post-dose 2), the anti-gE antibody concentration in 49 evaluable subjects was 2.4-fold (95% CI: 1.6; 3.7) above pre-vaccination level (Mean Geometric Increase). Median frequency of gE specific CD4[2+] T cells at Month 24 in 19 evaluable subjects in CMI subset remained above pre-vaccination level.

#### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Shingrix in one or more subsets of the paediatric population in prevention of Varicella Zoster Virus reactivation (see section 4.2 for information on paediatric use).

### **5.2 Pharmacokinetic properties**

Not applicable.

### **5.3 Preclinical safety data**

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

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sucrose  
Polysorbate 80 (E 433)  
Sodium dihydrogen phosphate dihydrate (E 339)  
Dipotassium phosphate (E 340)  
Dioleoyl phosphatidylcholine (E 322)  
Cholesterol  
Sodium chloride

Disodium phosphate anhydrous (E 339)  
Potassium dihydrogen phosphate (E 340)  
Water for injections

For adjuvant see section 2.

## 6.2 Incompatibilities

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

## 6.3 Shelf life

3 years

## 6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Store in the original package in order to protect from light.

Shingrix is to be administered as soon as possible after being removed from the refrigerator. However, stability data indicate that Shingrix is stable for 72 hours at temperatures between 8 °C and 37 °C. At the end of this period, Shingrix should be used immediately or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

## 6.5 Nature and contents of container

0.5 mL of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap.

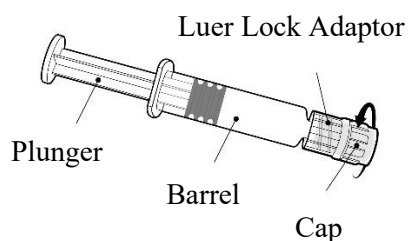
Shingrix is available in pack sizes of 1 and 10 syringes without needles.

Not all pack sizes may be marketed.

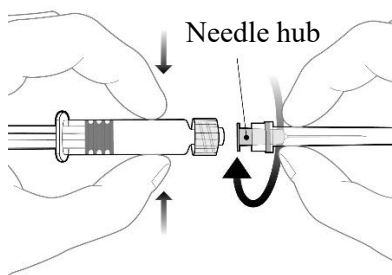
## 6.6 Special precautions for disposal and other handling

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

### Instructions for the pre-filled syringe



Hold the syringe by the barrel, not by the plunger.  
Unscrew the syringe cap by twisting it anticlockwise.



To attach the needle, connect the hub to the Luer Lock Adapter and rotate a quarter turn clockwise until you feel it lock.  
Do not pull the syringe plunger out of the barrel.  
If it happens, do not administer the vaccine.

### Disposal

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

## **7. MARKETING AUTHORISATION HOLDER**

GlaxoSmithKline Biologicals S.A.  
Rue de l'Institut 89  
B-1330 Rixensart  
Belgium

## **8. MARKETING AUTHORISATION NUMBERS**

EU/1/18/1272/003  
EU/1/18/1272/004

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 21 March 2018  
Date of latest renewal: 05 December 2022

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS FOR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCES AND  
MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer of the biological active substances

GlaxoSmithKline Biologicals SA  
Parc de la Noire Epine  
20, Avenue Fleming  
1300 Wavre  
BELGIUM

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Biologicals SA  
Rue de l'Institut, 89  
1330 Rixensart  
BELGIUM

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING  
AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND  
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.



**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

## **PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**1 VIAL AND 1 VIAL**  
**10 VIALS AND 10 VIALS**

### **1. NAME OF THE MEDICINAL PRODUCT**

Shingrix powder and suspension for suspension for injection  
Herpes zoster vaccine (recombinant, adjuvanted)

### **2. STATEMENT OF ACTIVE SUBSTANCE(S)**

After reconstitution, 1 dose (0.5 mL) contains 50 micrograms of recombinant Varicella Zoster Virus glycoprotein E adjuvanted with AS01<sub>B</sub>

### **3. LIST OF EXCIPIENTS**

Excipients:  
sucrose  
polysorbate 80  
sodium dihydrogen phosphate dihydrate  
dipotassium phosphate  
dioleoyl phosphatidylcholine  
cholesterol  
sodium chloride  
disodium phosphate anhydrous  
potassium dihydrogen phosphate  
water for injections  
See leaflet for further information.

### **4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and suspension for suspension for injection  
1 vial: powder (antigen)  
1 vial: suspension (adjuvant)

10 vials: powder (antigen)  
10 vials: suspension (adjuvant)

### **5. METHOD AND ROUTES OF ADMINISTRATION**

Read the package leaflet before use.  
Intramuscular use

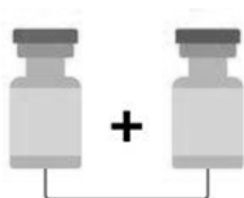
### **6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Powder and suspension to be reconstituted before administration

**Antigen      Adjuvant**



**1 dose (0.5 mL)**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.

Do not freeze.

Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

GlaxoSmithKline Biologicals s.a.

Rue de l'Institut 89

B-1330 Rixensart

Belgium

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/18/1272/001 – 1 vial and 1 vial

EU/1/18/1272/002 – 10 vials and 10 vials

**13. BATCH NUMBER**

LOT

**14. GENERAL CLASSIFICATION FOR SUPPLY**

<b>15. INSTRUCTIONS ON USE</b>
--------------------------------

<b>16. INFORMATION IN BRAILLE</b>
-----------------------------------

Justification for not including Braille accepted.

<b>17. UNIQUE IDENTIFIER – 2D BARCODE</b>
---

2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN

<b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b> <b>VIAL WITH POWDER LABEL</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION</b>
--

Antigen for Shingrix  
IM

<b>2. METHOD OF ADMINISTRATION</b>
------------------------------------

Mix with adjuvant

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

LOT

<b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b>
--

1 dose

<b>6. OTHER</b>
-----------------

<b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b> <b>VIAL WITH SUSPENSION LABEL</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION</b>
--

Adjuvant for Shingrix

<b>2. METHOD OF ADMINISTRATION</b>
------------------------------------

Mix with antigen

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

LOT

<b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b>
--

1 dose (0.5 mL)

<b>6. OTHER</b>
-----------------

## **PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**1 PRE-FILLED SYRINGE**  
**10 PRE-FILLED SYRINGES**

### **1. NAME OF THE MEDICINAL PRODUCT**

Shingrix suspension for injection in pre-filled syringe  
Herpes zoster vaccine (recombinant, adjuvanted)

### **2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One dose (0.5 mL) contains 50 micrograms of recombinant Varicella Zoster Virus glycoprotein E adjuvanted with AS01<sub>B</sub>

### **3. LIST OF EXCIPIENTS**

Excipients:  
sucrose  
polysorbate 80  
sodium dihydrogen phosphate dihydrate  
dipotassium phosphate  
dioleoyl phosphatidylcholine  
cholesterol  
sodium chloride  
disodium phosphate anhydrous  
potassium dihydrogen phosphate  
water for injections  
See leaflet for further information.

### **4. PHARMACEUTICAL FORM AND CONTENTS**

Suspension for injection  
1 pre-filled syringe  
1 dose (0.5 mL)

10 pre-filled syringes  
10 x 1 dose (0.5 mL)

### **5. METHOD AND ROUTES OF ADMINISTRATION**

Read the package leaflet before use.  
Intramuscular use

### **6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.



**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.

Do not freeze.

Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

GlaxoSmithKline Biologicals s.a.

Rue de l'Institut 89

B-1330 Rixensart

Belgium

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/18/1272/003 – pack of 1 without needle

EU/1/18/1272/004 – pack of 10 without needle

**13. BATCH NUMBER**

LOT

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN

<b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b> <b>PRE-FILLED SYRINGE LABEL</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</b>
--

Shingrix injection  
Herpes Zoster vaccine  
IM

<b>2. METHOD OF ADMINISTRATION</b>
------------------------------------

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

LOT

<b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b>
--

1 dose  
(0.5 mL)

<b>6. OTHER</b>
-----------------

## **B. PACKAGE LEAFLET**

## **Package leaflet: Information for the user**

### **Shingrix powder and suspension for suspension for injection**

Herpes zoster vaccine (recombinant, adjuvanted)

**Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Shingrix is and what it is used for
2. What you need to know before you receive Shingrix
3. How Shingrix is given
4. Possible side effects
5. How to store Shingrix
6. Contents of the pack and other information

#### **1. What Shingrix is and what it is used for**

##### **What Shingrix is used for**

Shingrix is a vaccine that helps to protect adults against shingles (herpes zoster) and post-herpetic neuralgia (PHN), the long-lasting nerve pain that follows shingles.

Shingrix is given to:

- adults 50 years and above;
- adults 18 years and above who are at increased risk of shingles.

Shingrix cannot be used to prevent chickenpox (varicella).

##### **What shingles is**

- Shingles is a rash with blisters that is often painful. It usually occurs in one part of the body and can last for several weeks.
- 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, if your immune system (the body's natural defences) becomes weaker (due to age, an illness or a medicine you are taking), the virus can cause shingles.

##### **Complications related to shingles**

Shingles may lead to complications.

The most common complication of shingles is:

- long-lasting nerve pain – called post-herpetic neuralgia or PHN. After the shingles blisters heal, you may get pain which can last for months or years and may be severe.

Other complications of shingles are:

- scars where the blisters have been.
- skin infections, weakness, muscle paralysis and loss of hearing or vision – these are less common.

##### **How Shingrix works**

Shingrix reminds your body about the virus that causes shingles. This helps your immune system (the body's natural defences) stay prepared to fight the virus and protect you against shingles and its complications.

## **2. What you need to know before you receive Shingrix**

### **You must not be given Shingrix if**

- you are allergic to the active substances or any of the other ingredients of this vaccine (listed in section 6). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

You must not be given Shingrix if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist.

### **Warnings and precautions**

Talk to your doctor or pharmacist before you receive Shingrix if:

- you have a severe infection with a high temperature (fever). In these cases, the vaccination may have to be postponed until you have recovered. A minor infection such as a cold should not be a problem, but talk to your doctor first;
- you have a bleeding problem or bruise easily.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before you receive Shingrix.

Fainting can occur before or after any needle injection. Therefore tell the doctor or nurse if you fainted with a previous injection.

Shingrix cannot be used as a treatment if you already have shingles or shingles-related complications.

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

### **Other medicines and Shingrix**

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription, or have recently received any other vaccine.

Shingrix can be given at the same time as other vaccines such as seasonal influenza vaccine (inactivated, unadjuvanted), 23-valent pneumococcal polysaccharide vaccine, 13-valent pneumococcal conjugate vaccine, reduced antigen diphtheria tetanus acellular pertussis vaccine, COVID-19 mRNA vaccine, or respiratory syncytial virus (RSV) vaccine (recombinant, adjuvanted). A different injection site will be used for each vaccine.

You may be more likely to experience fever and/or shivering when 23-valent pneumococcal polysaccharide vaccine is given at the same time as Shingrix.

You may be more likely to experience chills, tiredness, fever, stomach and digestive complaints (including nausea, vomiting, diarrhoea and/or stomach pain), headache, muscle pain, or joint pain when a COVID-19 mRNA vaccine is given at the same time as Shingrix.

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this vaccine.

### **Driving and using machines**

Some of the effects mentioned below in section 4 “Possible side effects” may temporarily affect the ability to drive or use machines. Do not drive or use machines if you are feeling unwell.

**Shingrix contains polysorbate 80, sodium and potassium**

This medicine contains 0.08 mg of polysorbate 80 per dose. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

This medicine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially 'potassium-free'.

**3. How Shingrix is given**

- Shingrix is given as an injection into a muscle (usually in the upper arm).
- You will receive 2 injections 2 months apart. If flexibility in the vaccination schedule is necessary, the second dose can be administered between 2 and 6 months after the first dose. Based on your medical condition, your doctor may also recommend that you receive the second injection 1 month after the first injection.
- You will be informed when you should come back for the second dose of Shingrix.

Make sure you finish the complete vaccination course. This will maximise the protection offered by Shingrix.

Shingrix can be given if you have already been vaccinated with a live attenuated herpes zoster vaccine. Speak to your doctor for more information.

**4. Possible side effects**

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

**Side effects reported during clinical trials and after marketing of Shingrix:**

**Very common** (may occur with more than 1 in 10 doses of the vaccine):

- headache
- stomach and digestive complaints (including nausea, vomiting, diarrhoea and/or stomach pain)
- muscle pain (myalgia)
- pain, redness and swelling where the injection is given
- feeling tired
- chills
- fever

**Common** (may occur with up to 1 in 10 doses of the vaccine):

- itching where the injection is given (pruritus)
- generally feeling unwell

**Uncommon** (may occur with up to 1 in 100 doses of vaccine)

- swollen glands in the neck, armpit or groin
- joint pain

**Rare** (may occur with up to 1 in 1 000 doses of the vaccine)

- allergic reactions including rash, hives (urticaria), swelling of the face, tongue or throat which may cause difficulty in swallowing or breathing (angioedema)

**Very rare** (may occur with up to 1 in 10 000 doses of the vaccine)

- a neurological disorder that usually starts with pins and needles and weakness of the limbs and may progress to paralysis of part or all of the body (Guillain-Barré syndrome)

Most of these side effects are mild to moderate in intensity and are not long-lasting.

Immunocompromised adults aged 18-49 years may experience more side effects compared to immunocompromised adults aged  $\geq 50$  years.

Adults aged 50-69 years may experience more side effects compared to adults aged  $\geq 70$  years.

### Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Shingrix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator ( $2^{\circ}\text{C} - 8^{\circ}\text{C}$ ). Do not freeze.

Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Shingrix contains

- The active substances are:

After reconstitution, one dose (0.5 mL) contains:

Varicella Zoster Virus <sup>1</sup> glycoprotein E antigen <sup>2</sup>	50 micrograms
---	---------------

<sup>1</sup> Varicella Zoster Virus = VZV

<sup>2</sup> adjuvanted with AS01<sub>B</sub> containing:

plant extract <i>Quillaja saponaria</i> Molina, fraction 21 (QS-21)	50 micrograms
3-O-desacyl-4'-monophosphoryl lipid A (MPL) from <i>Salmonella minnesota</i>	50 micrograms

The glycoprotein E is a protein present in the Varicella Zoster Virus. This protein is not infectious.

The adjuvant (AS01<sub>B</sub>) is used to improve the body's response to the vaccine.

- The other ingredients are:
  - **Powder:** Sucrose, polysorbate 80 (E 433), sodium dihydrogen phosphate dihydrate (E 339), dipotassium phosphate (E 340).
  - **Suspension:** Dioleoyl phosphatidylcholine (E 322), cholesterol, sodium chloride, disodium phosphate anhydrous (E 339), potassium dihydrogen phosphate (E 340) and water for injections.

See section 2 "Shingrix contains polysorbate 80, sodium and potassium".

### What Shingrix looks like and contents of the pack

Powder and suspension for suspension for injection. The powder is white.



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

One pack of Shingrix consists of:

- Powder (antigen) for 1 dose in a vial
- Suspension (adjuvant) for 1 dose in a vial

Shingrix is available in a pack size of 1 vial of powder and 1 vial of suspension or in a pack size of 10 vials of powder and 10 vials of suspension.

Not all pack sizes may be marketed.

#### **Marketing Authorisation Holder and Manufacturer**

GlaxoSmithKline Biologicals s.a.  
Rue de l'Institut 89  
B-1330 Rixensart  
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

#### **België/Belgique/Belgien**

GlaxoSmithKline Pharmaceuticals s.a./n.v.  
Tél/Tel: + 32 (0) 10 85 52 00

#### **Lietuva**

GlaxoSmithKline Biologicals SA  
Tel: +370 80000334

#### **България**

GlaxoSmithKline Biologicals SA  
Тел.: +359 80018205

#### **Luxembourg/Luxemburg**

GlaxoSmithKline Pharmaceuticals s.a./n.v.  
Belgique/Belgien  
Tél/Tel: + 32 (0) 10 85 52 00

#### **Česká republika**

GlaxoSmithKline s.r.o.  
Tel: + 420 2 22 00 11 11  
cz.info@gsk.com

#### **Magyarország**

GlaxoSmithKline Biologicals SA  
Tel.: +36 80088309

#### **Danmark**

GlaxoSmithKline Pharma A/S  
Tlf.: + 45 36 35 91 00  
dk-info@gsk.com

#### **Malta**

GlaxoSmithKline Biologicals SA  
Tel: +356 80065004

#### **Deutschland**

GlaxoSmithKline GmbH & Co. KG  
Tel: + 49 (0)89 360448701  
produkt.info@gsk.com

#### **Nederland**

GlaxoSmithKline BV  
Tel: + 31 (0)33 2081100

#### **Eesti**

GlaxoSmithKline Biologicals SA  
Tel: +372 8002640

#### **Norge**

GlaxoSmithKline AS  
Tlf: + 47 22 70 20 00

#### **Ελλάδα**

GlaxoSmithKline Μονοπρόσωπη Α.Ε.Β.Ε  
Τηλ: + 30 210 68 82 100

#### **Österreich**

GlaxoSmithKline Pharma GmbH  
Tel: + 43 (0)1 97075 0  
at.info@gsk.com

#### **España**

#### **Polska**

GlaxoSmithKline, S.A.  
Tel: + 34 900 202 700  
es-ci@gsk.com

**France**

Laboratoire GlaxoSmithKline  
Tél: + 33 (0) 1 39 17 84 44  
diam@gsk.com

**Hrvatska**

GlaxoSmithKline Biologicals SA  
Tel: +385 800787089

**Ireland**

GlaxoSmithKline (Ireland) Ltd  
Tel: + 353 (0)1 495 5000

**Ísland**

Vistor hf.  
Sími: +354 535 7000

**Italia**

GlaxoSmithKline S.p.A.  
Tel: + 39 (0)45 7741 111

**Κύπρος**

GlaxoSmithKline Biologicals SA  
Τηλ: +357 80070017

**Latvija**

GlaxoSmithKline Biologicals SA  
Tel: +371 80205045

GSK Services Sp. z o.o.  
Tel.: + 48 (22) 576 9000

**Portugal**

GlaxoSmithKline - Produtos Farmacêuticos, Lda.  
Tel: + 351 21 412 95 00  
FI.PT@gsk.com

**România**

GlaxoSmithKline Biologicals SA  
Tel: +40 800672524

**Slovenija**

GlaxoSmithKline Biologicals SA  
Tel: +386 80688869

**Slovenská republika**

GlaxoSmithKline Biologicals SA  
Tel: +421 800500589

**Suomi/Finland**

GlaxoSmithKline Oy  
Puh/Tel: + 358 10 30 30 30

**Sverige**

GlaxoSmithKline AB  
Tel: + 46 (0)8 638 93 00  
info.produkt@gsk.com

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**Other sources of information**

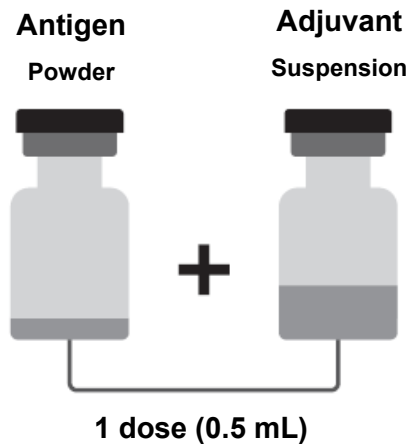
Detailed information on this medicine is available on the European Medicines Agency web site:  
<https://www.ema.europa.eu>.

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The following information is intended for healthcare professionals only:

Shingrix is presented as a vial with a brown flip-off cap containing the powder (antigen) and a vial with a blue-green flip-off cap containing the suspension (adjuvant).

The powder and the suspension must be reconstituted prior to administration.



The 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 syringe with a suitable needle (21G to 25G).
2. Add the entire contents of the syringe into the vial containing the powder.
3. Shake gently until the 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 – 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 the syringe.
2. Change the needle so that you are using a new needle to administer the vaccine.

#### Disposal

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

## **Package leaflet: Information for the user**

### **Shingrix suspension for injection in pre-filled syringe** Herpes zoster vaccine (recombinant, adjuvanted)

**Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Shingrix is and what it is used for
2. What you need to know before you receive Shingrix
3. How Shingrix is given
4. Possible side effects
5. How to store Shingrix
6. Contents of the pack and other information

#### **1. What Shingrix is and what it is used for**

##### **What Shingrix is used for**

Shingrix is a vaccine that helps to protect adults against shingles (herpes zoster) and post-herpetic neuralgia (PHN), the long-lasting nerve pain that follows shingles.

Shingrix is given to:

- adults 50 years and above;
- adults 18 years and above who are at increased risk of shingles.

Shingrix cannot be used to prevent chickenpox (varicella).

##### **What shingles is**

- Shingles is a rash with blisters that is often painful. It usually occurs in one part of the body and can last for several weeks.
- 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, if your immune system (the body's natural defences) becomes weaker (due to age, an illness or a medicine you are taking), the virus can cause shingles.

##### **Complications related to shingles**

Shingles may lead to complications.

The most common complication of shingles is:

- long-lasting nerve pain – called post-herpetic neuralgia or PHN. After the shingles blisters heal, you may get pain which can last for months or years and may be severe.

Other complications of shingles are:

- scars where the blisters have been.
- skin infections, weakness, muscle paralysis and loss of hearing or vision – these are less common.

##### **How Shingrix works**

Shingrix reminds your body about the virus that causes shingles. This helps your immune system (the body's natural defences) stay prepared to fight the virus and protect you against shingles and its complications.

## **2. What you need to know before you receive Shingrix**

### **You must not be given Shingrix if**

- you are allergic to the active substances or any of the other ingredients of this vaccine (listed in section 6). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

You must not be given Shingrix if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist.

### **Warnings and precautions**

Talk to your doctor or pharmacist before you receive Shingrix if:

- you have a severe infection with a high temperature (fever). In these cases, the vaccination may have to be postponed until you have recovered. A minor infection such as a cold should not be a problem, but talk to your doctor first;
- you have a bleeding problem or bruise easily.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before you receive Shingrix.

Fainting can occur before or after any needle injection. Therefore tell the doctor or nurse if you fainted with a previous injection.

Shingrix cannot be used as a treatment if you already have shingles or shingles-related complications.

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

### **Other medicines and Shingrix**

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription, or have recently received any other vaccine.

Shingrix can be given at the same time as other vaccines such as seasonal influenza vaccine (inactivated, unadjuvanted), 23-valent pneumococcal polysaccharide vaccine, 13-valent pneumococcal conjugate vaccine, reduced antigen diphtheria tetanus acellular pertussis vaccine, COVID-19 mRNA vaccine, or respiratory syncytial virus (RSV) vaccine (recombinant, adjuvanted). A different injection site will be used for each vaccine.

You may be more likely to experience fever and/or shivering when 23-valent pneumococcal polysaccharide vaccine is given at the same time as Shingrix.

You may be more likely to experience chills, tiredness, fever, stomach and digestive complaints (including nausea, vomiting, diarrhoea and/or stomach pain), headache, muscle pain, or joint pain when a COVID-19 mRNA vaccine is given at the same time as Shingrix.

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this vaccine.

### **Driving and using machines**

Some of the effects mentioned below in section 4 “Possible side effects” may temporarily affect the ability to drive or use machines. Do not drive or use machines if you are feeling unwell.

**Shingrix contains polysorbate 80, sodium and potassium**

This medicine contains 0.08 mg of polysorbate 80 per dose. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

This medicine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially 'potassium-free'.

**3. How Shingrix is given**

- Shingrix is given as an injection into a muscle (usually in the upper arm).
- You will receive 2 injections 2 months apart. If flexibility in the vaccination schedule is necessary, the second dose can be administered between 2 and 6 months after the first dose. Based on your medical condition, your doctor may also recommend that you receive the second injection 1 month after the first injection.
- You will be informed when you should come back for the second dose of Shingrix.

Make sure you finish the complete vaccination course. This will maximise the protection offered by Shingrix.

Shingrix can be given if you have already been vaccinated with a live attenuated herpes zoster vaccine. Speak to your doctor for more information.

**4. Possible side effects**

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

**Side effects reported during clinical trials and after marketing of Shingrix:**

**Very common** (may occur with more than 1 in 10 doses of the vaccine):

- headache
- stomach and digestive complaints (including nausea, vomiting, diarrhoea and/or stomach pain)
- muscle pain (myalgia)
- pain, redness and swelling where the injection is given
- feeling tired
- chills
- fever

**Common** (may occur with up to 1 in 10 doses of the vaccine):

- itching where the injection is given (pruritus)
- generally feeling unwell

**Uncommon** (may occur with up to 1 in 100 doses of vaccine)

- swollen glands in the neck, armpit or groin
- joint pain

**Rare** (may occur with up to 1 in 1 000 doses of the vaccine)

- allergic reactions including rash, hives (urticaria), swelling of the face, tongue or throat which may cause difficulty in swallowing or breathing (angioedema)

**Very rare** (may occur with up to 1 in 10 000 doses of the vaccine)

- a neurological disorder that usually starts with pins and needles and weakness of the limbs and may progress to paralysis of part or all of the body (Guillain-Barré syndrome)

Most of these side effects are mild to moderate in intensity and are not long-lasting.

Immunocompromised adults aged 18-49 years may experience more side effects compared to immunocompromised adults aged  $\geq 50$  years.

Adults aged 50-69 years may experience more side effects compared to adults aged  $\geq 70$  years.

### Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Shingrix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator ( $2^{\circ}\text{C} - 8^{\circ}\text{C}$ ). Do not freeze.

Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Shingrix contains

- The active substances are:

One dose (0.5 mL) contains:

Varicella Zoster Virus <sup>1</sup> glycoprotein E antigen <sup>2</sup>	50 micrograms
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<sup>1</sup> Varicella Zoster Virus = VZV

<sup>2</sup> adjuvanted with AS01<sub>B</sub> containing:

plant extract <i>Quillaja saponaria</i> Molina, fraction 21 (QS-21)	50 micrograms
3-O-desacyl-4'-monophosphoryl lipid A (MPL) from <i>Salmonella minnesota</i>	50 micrograms

The glycoprotein E is a protein present in the Varicella Zoster Virus. This protein is not infectious.

The adjuvant (AS01<sub>B</sub>) is used to improve the body's response to the vaccine.

- The other ingredients are:

Sucrose, polysorbate 80 (E 433), sodium dihydrogen phosphate dihydrate (E 339), dipotassium phosphate (E 340), dioleoyl phosphatidylcholine (E 322), cholesterol, sodium chloride, disodium phosphate anhydrous (E 339), potassium dihydrogen phosphate (E 340) and water for injections. See section 2 "Shingrix contains polysorbate 80, sodium and potassium".

### What Shingrix looks like and contents of the pack

Suspension for injection (injection) in pre-filled syringe.

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

Shingrix is available in 1-dose pre-filled syringe without needles, in a pack size of 1 or 10.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

GlaxoSmithKline Biologicals s.a.  
Rue de l'Institut 89  
B-1330 Rixensart  
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**

GlaxoSmithKline Pharmaceuticals s.a./n.v.  
Tél/Tel: + 32 (0) 10 85 52 00

**Lietuva**

GlaxoSmithKline Biologicals SA  
Tel: +370 80000334

**България**

GlaxoSmithKline Biologicals SA  
Тел.: +359 80018205

**Luxembourg/Luxemburg**

GlaxoSmithKline Pharmaceuticals s.a./n.v.  
Belgique/Belgien  
Tél/Tel: + 32 (0) 10 85 52 00

**Česká republika**

GlaxoSmithKline s.r.o.  
Tel: + 420 2 22 00 11 11  
cz.info@gsk.com

**Magyarország**

GlaxoSmithKline Biologicals SA  
Tel.: +36 80088309

**Danmark**

GlaxoSmithKline Pharma A/S  
Tlf.: + 45 36 35 91 00  
dk-info@gsk.com

**Malta**

GlaxoSmithKline Biologicals SA  
Tel: +356 80065004

**Deutschland**

GlaxoSmithKline GmbH & Co. KG  
Tel: + 49 (0)89 360448701  
produkt.info@gsk.com

**Nederland**

GlaxoSmithKline BV  
Tel: + 31 (0)33 2081100

**Eesti**

GlaxoSmithKline Biologicals SA  
Tel: +372 8002640

**Norge**

GlaxoSmithKline AS  
Tlf: + 47 22 70 20 00

**Ελλάδα**

GlaxoSmithKline Μονοπρόσωπη Α.Ε.Β.Ε  
Τηλ: + 30 210 68 82 100

**Österreich**

GlaxoSmithKline Pharma GmbH  
Tel: + 43 (0)1 97075 0  
at.info@gsk.com

**España**

GlaxoSmithKline, S.A.  
Tel: + 34 900 202 700  
es-ci@gsk.com

**Polska**

GSK Services Sp. z o.o.  
Tel.: + 48 (22) 576 9000

**France**

Laboratoire GlaxoSmithKline  
Tél: + 33 (0) 1 39 17 84 44

**Portugal**

GlaxoSmithKline - Produtos Farmacêuticos, Lda.  
Tel: + 351 21 412 95 00



diam@gsk.com

FI.PT@gsk.com

**Hrvatska**

GlaxoSmithKline Biologicals SA  
Tel: +385 800787089

**România**

GlaxoSmithKline Biologicals SA  
Tel: +40 800672524

**Ireland**

GlaxoSmithKline (Ireland) Ltd  
Tel: + 353 (0)1 495 5000

**Slovenija**

GlaxoSmithKline Biologicals SA  
Tel: +386 80688869

**Ísland**

Vistor hf.  
Sími: +354 535 7000

**Slovenská republika**

GlaxoSmithKline Biologicals SA  
Tel: +421 800500589

**Italia**

GlaxoSmithKline S.p.A.  
Tel: + 39 (0)45 7741 111

**Suomi/Finland**

GlaxoSmithKline Oy  
Puh/Tel: + 358 10 30 30 30

**Κύπρος**

GlaxoSmithKline Biologicals SA  
Τηλ: +357 80070017

**Sverige**

GlaxoSmithKline AB  
Tel: + 46 (0)8 638 93 00  
info.produkt@gsk.com

**Latvija**

GlaxoSmithKline Biologicals SA  
Tel: +371 80205045

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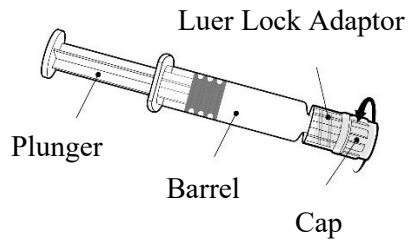
**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<https://www.ema.europa.eu>.

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The following information is intended for healthcare professionals only:

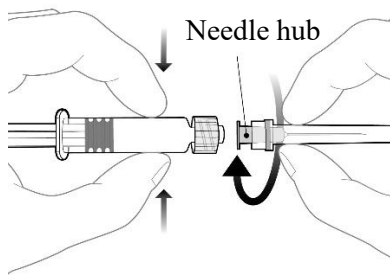
The vaccine should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not administer the vaccine.

Instructions for the pre-filled syringe



Hold the syringe by the barrel, not by the plunger.

Unscrew the syringe cap by twisting it anticlockwise.



To attach the needle, connect the hub to the Luer Lock Adaptor and rotate a quarter turn clockwise until you feel it lock.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

### Disposal

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