

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems

AUSTRALIAN PRODUCT INFORMATION

SHINGRIX (recombinant Varicella Zoster Virus glycoprotein E antigen) powder and suspension for suspension for injection

1 NAME OF THE MEDICINE

Recombinant Varicella Zoster Virus glycoprotein E antigen (AS01_B adjuvanted vaccine)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 mL) contains 50 micrograms of gE antigen¹ adjuvanted with AS01_B².

¹ Varicella Zoster Virus (VZV) glycoprotein E (gE) produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells

² The GlaxoSmithKline proprietary AS01_B Adjuvant System is composed of the plant extract *Quillaja saponaria* saponin (QS-21) (50 micrograms) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* (50 micrograms).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

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 the prevention of herpes zoster (HZ) and post-herpetic neuralgia in:

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

4.2 DOSE AND METHOD OF ADMINISTRATION

The immunisation schedules for SHINGRIX should be based on official recommendations.

Further guidance regarding the use of vaccines can be found in the Australian Immunisation Handbook.

Dosage:

The primary vaccination schedule consists of two doses of 0.5 mL each; an initial dose followed by a second dose 2 to 6 months later.

For subjects who are immunodeficient, immunosuppressed or likely to become immunosuppressed due to known disease or therapy, and who 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 PHARMACODYNAMIC PROPERTIES, Clinical trials).

The need for booster doses has not been established.

SHINGRIX can be given with the same schedule in individuals previously vaccinated with live attenuated herpes zoster (HZ) vaccine, in accordance with local recommendations (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

SHINGRIX is not indicated for prevention of primary varicella infection (chickenpox) or for treatment of herpes zoster or post-herpetic neuralgia (PHN).

Method of administration:

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

Instructions for Use and Handling:

The powder and suspension should be inspected visually for any particulate matter and/or variation to the expected appearance (i.e. white powder and opalescent, colourless to pale brownish liquid). 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 the syringe.
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.

SHINGRIX is for single use in one patient only.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substances or to any component of the vaccine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Prior to immunisation:

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

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

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

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

In a post-marketing observational study in individuals aged 65 years or older, an increased risk of Guillain-Barré syndrome (estimated 3 excess cases per million doses administered) was observed during the 42 days following vaccination with SHINGRIX. Available information is insufficient to determine a causal relationship with SHINGRIX.

Precautions for use:

Do not administer the vaccine intravascularly, intradermally or subcutaneously.

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

SHINGRIX 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. It is important that procedures are in place to prevent injury from faints and to manage syncopal reactions.

There are no safety, immunogenicity or efficacy data to support interchangeability of SHINGRIX with other HZ vaccines.

There are limited data to support the use of SHINGRIX in individuals with a history of HZ and in frail individuals including those with multiple comorbidities. Healthcare professionals therefore need to weigh the benefits and risks of HZ vaccination on an individual basis.

As with other vaccines, an adequate immune response may not be elicited in these individuals. The administration of SHINGRIX to immunocompromised subjects should be based on careful consideration of potential benefits and risks.

Use in the elderly

There are no special precautions for use in the elderly.

Paediatric use

The safety and efficacy of SHINGRIX have not been established in children and adolescents.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Use with other vaccines

SHINGRIX can be given concomitantly with either unadjuvanted seasonal influenza vaccine, 23-valent pneumococcal polysaccharide vaccine (PPV23) or reduced antigen diphtheria-tetanus-acellular pertussis vaccine (dTpa) (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

The adverse reactions of fever and shivering were more frequent when PPV23 vaccine was co-administered with SHINGRIX compared to when SHINGRIX was given alone (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

The vaccines should always be administered at different injection sites.

No data are currently available regarding concomitant use with other vaccines, including the adjuvanted seasonal influenza vaccine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Repeated exposure of male and female rats to SHINGRIX (0.1 and 0.2 mL respectively) by IM injection on 42, 28 and 14 days prior to mating (male) and 28 and 14 days prior to mating (female) had no effects on mating or fertility.

Use in pregnancy

(Pregnancy Category B2)

There are no data on the use of SHINGRIX in pregnant women.

In a reproductive and developmental toxicity study, female rats were administered SHINGRIX or the AS01_B adjuvant alone by intramuscular injection 28 and 14 days prior to mating, on gestation Days 3, 8, 11, and 15, and on lactation Day 7. The total dose was 0.2 mL on each occasion (a single human dose of SHINGRIX is 0.5 mL). No adverse effects on preweaning development up to post-natal Day 25 were observed. There were no vaccine-related foetal malformations or variations.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of SHINGRIX on the ability to drive and use machines have been performed.

However, some of the undesirable effects mentioned in Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) may temporarily influence the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

More than 17,000 adults aged 50 through 96 years of age received at least one dose of SHINGRIX in 17 clinical studies. The incidence of solicited local and general symptoms was

higher in subjects who received SHINGRIX than in subjects who received control (placebo or other vaccines). SHINGRIX was generally well tolerated.

Additionally, in clinical studies, 1,587 subjects \geq 18 years of age who are immunodeficient or immunosuppressed due to disease or therapy (referred to as immunocompromised (IC)), were vaccinated with at least 1 dose of Shingrix. The reported adverse reactions were consistent with those reported clinical trial adverse reactions of adults 50 years of age and older.

Overall, there was a higher incidence of some adverse reactions in younger age groups. However, the overall frequency and severity of these events did not indicate a clinically meaningful different reactogenicity profile in the younger age strata. In IC adult studies, there was a higher incidence of pain at the injection site, fatigue, myalgia, headache, shivering and fever in subjects aged 18 to 49 years compared with those aged 50 years and older. In older adult studies, there was a higher incidence of pain and swelling at the injection site, fatigue, myalgia, headache, shivering, fever and gastrointestinal symptoms in subjects aged 50 to 69 years compared with those aged 70 years and older.

Clinical trial data

Adults aged 50 years and older

The safety profile presented below is based on pooled data from 2 placebo-controlled clinical studies (ZOE-50 and ZOE-70) involving 29,305 subjects aged 50 years and older who received at least one dose of SHINGRIX (n = 14,645) or saline placebo (n = 14,660) administered according to a 0, 2-month schedule. These studies were conducted in Europe, North America, Latin America, Asia and Australia.

Solicited Adverse Events

In both studies, data on solicited local and general adverse events were collected using standardized diary cards for 7 days following each vaccine dose or placebo (i.e., day of vaccination and the next 6 days) in a subset of subjects (n = 4,886 receiving SHINGRIX, n = 4,881 receiving placebo with at least 1 documented dose). Across both studies, the percentages of subjects aged 50 years and older reporting each solicited local adverse reaction and each solicited general adverse event following administration of SHINGRIX (both doses combined) were pain (78.0%), redness (38.1%), and swelling (25.9%); and myalgia (44.7%), fatigue (44.5%), headache (37.7%), shivering (26.8%), fever (20.5%), and gastrointestinal symptoms (17.3%), respectively.

The reported frequencies of specific solicited local adverse reactions and general adverse events (overall per subject), by age group, from the 2 studies are presented in Table 1.

Table 1: Percentage of Subjects with Solicited Local Adverse Reactions and General Adverse Events within 7 Days^a of Vaccination in Adults Aged 50 to 59 Years, 60 to 69 Years, and 70 Years and Older^b (Total Vaccinated Cohort with 7-Day Diary Card)

	Aged 50 - 59 Years		Aged 60 - 69 Years		Aged \geq 70 Years	
	SHINGRIX	Placebo ^c	SHINGRIX	Placebo ^c	SHINGRIX	Placebo ^c
	%	%	%	%	%	%
Local Adverse Reactions	n = 1,315	n = 1,312	n = 1,311	n = 1,305	n = 2,258	n = 2,263

	Aged 50 - 59 Years		Aged 60 - 69 Years		Aged ≥70 Years	
	SHINGRIX	Placebo ^c	SHINGRIX	Placebo ^c	SHINGRIX	Placebo ^c
	%	%	%	%	%	%
Pain	88.4	14.4	82.8	11.1	69.2	8.8
Pain, Grade 3 ^d	10.3	0.5	6.9	0.5	4.0	0.2
Redness	38.7	1.2	38.4	1.6	37.7	1.2
Redness, >100 mm	2.8	0.0	2.6	0.0	3.1	0.0
Swelling	30.5	0.8	26.5	1.0	23.0	1.1
Swelling, >100 mm	1.1	0.0	0.5	0.0	1.3	0.0
General Adverse Events	n = 1,315	n = 1,312	n = 1,309	n = 1,305	n = 2,252	n = 2,264
Myalgia	56.9	15.2	49.0	11.2	35.1	9.9
Myalgia, Grade 3 ^e	8.9	0.9	5.3	0.8	2.8	0.4
Fatigue	57.0	19.8	45.7	16.8	36.6	14.4
Fatigue, Grade 3 ^e	8.5	1.8	5.0	0.8	3.5	0.8
Headache	50.6	21.6	39.6	15.6	29.0	11.8
Headache, Grade 3 ^e	6.0	1.7	3.7	0.2	1.5	0.4
Shivering	35.8	7.4	30.3	5.7	19.5	4.9
Shivering, Grade 3 ^e	6.8	0.2	4.5	0.3	2.2	0.3
Fever	27.8	3.0	23.9	3.4	14.3	2.7
Fever, Grade 3 ^f	0.4	0.2	0.5	0.2	0.1	0.1
GI ^g	24.3	10.7	16.7	8.7	13.5	7.6
GI, Grade 3 ^e	2.1	0.7	0.9	0.6	1.2	0.4

Total vaccinated cohort for safety included all subjects with at least 1 documented dose (n).

^a 7 days included day of vaccination and the subsequent 6 days.

^b Data for subjects aged 50 to 59 years and 60 to 69 years are based on ZOE -50. Data for subjects 70 years and older are based on pooled data from ZOE-50 and ZOE-70.

^c Placebo was a saline solution.

^d Grade 3 pain: Defined as significant pain at rest; prevents normal everyday activities.

^e Grade 3 myalgia, fatigue, headache, shivering, GI: Defined as preventing normal activity.

^f Fever defined as ≥37.5°C for oral, axillary, or tympanic route, or ≥38°C for rectal route; Grade 3 fever defined as >39.0°C

^g GI = Gastrointestinal symptoms including nausea, vomiting, diarrhea, and/or abdominal pain.

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

The majority of solicited local adverse reactions and general adverse events seen with SHINGRIX had a median duration of 2 to 3 days.

There were no differences in the proportions of subjects reporting any or grade 3 solicited local reactions between Dose 1 and Dose 2. Headache and shivering were reported more frequently by subjects after Dose 2 (28.2% and 21.4%, respectively) compared with Dose 1 (24.4% and 13.8%, respectively). Grade 3 solicited general adverse events (headache, shivering, myalgia, and fatigue) were reported more frequently by subjects after Dose 2 (2.3%, 3.1%, 3.6%, and 3.5%, respectively) compared with Dose 1 (1.4%, 1.4%, 2.3%, and 2.4%, respectively).

Unsolicited Adverse Events

In both studies, unsolicited adverse events occurring within 30 days of vaccination were reported in 50.5% and 32.0% of subjects who received SHINGRIX (n = 14,645) and placebo (n = 14,660), respectively (Total Vaccinated Cohort). Unsolicited adverse events that occurred in $\geq 1\%$ of recipients of SHINGRIX and at a rate at least 1.5-fold higher than placebo included chills (3.5% versus 0.2%), injection site pruritus (2.2% versus 0.2%), and malaise (1.7% versus 0.3%), arthralgia (1.7% versus 1.2%), nausea (1.4% versus 0.5%), and dizziness (1.2% versus 0.8%).

Gout (including gouty arthritis) was reported by 0.18% (n = 27) versus 0.05% (n = 8) of subjects who received SHINGRIX and placebo, respectively, within 30 days of vaccination; available information is insufficient to determine a causal relationship with SHINGRIX.

In a clinical study where 119 subjects were vaccinated with SHINGRIX following a 0, 6-month schedule, the safety profile was similar to that observed in subjects vaccinated with SHINGRIX following a 0, 2-month schedule.

Potential Immune-Mediated Diseases

In the 2 studies, new onset potential immune-mediated diseases (pIMDs) or exacerbation of existing pIMDs were reported for 0.6% of subjects who received SHINGRIX and 0.7% of subjects who received placebo from the first administered dose up to 1 year post last vaccination. The most frequently reported pIMDs occurred with comparable frequencies in the group receiving SHINGRIX and the placebo group.

Immunocompromised (IC) adults aged 18 years and older

In early phase I/II clinical studies Zoster-001 and Zoster-015, the co-primary objectives were to evaluate the safety and reactogenicity of HZ vaccine formulations in subjects ≥ 18 years of age with a selected IC condition (autologous hematopoietic stem cell transplant (auHSCT) and HIV infection, respectively). More than half of the subjects who participated in Zoster-001 and Zoster-015 (54%) were ≥ 50 years of age. With the limited number of subjects (n = 164), no safety concerns were identified as evaluated one year post-vaccination (see PHARMACODYNAMIC PROPERTIES, Clinical trials).

The safety of SHINGRIX was also evaluated in 4 placebo-controlled phase II/III clinical studies of subjects aged 18 years and older who were immunocompromised. Subjects in the total vaccinated cohort received at least 1 dose (administered according to a 0- and 1-2-month schedule) of SHINGRIX or placebo, as follows: auHSCT recipients (n = 922 or n = 924, respectively); renal transplant recipients on chronic immunosuppressive treatment (n = 132 or n = 132, respectively); subjects with hematologic malignancies during a cancer therapy course or after the full cancer therapy course (n = 283 or n = 279, respectively); and subjects with solid tumours undergoing chemotherapy (n = 117 or n = 115, respectively). The methodology for evaluating solicited adverse reactions, unsolicited

adverse events, serious adverse events, deaths, and pIMDs across these studies was similar to those in the ZOE-50 and ZOE-70 studies.

Solicited Adverse Reactions

Across the 4 studies, the majority of solicited local and general adverse reactions seen with SHINGRIX had a median duration of 3 to 4 days. The reported frequencies of specific solicited local and general adverse reactions (overall per subject) by age group across the 4 studies are presented in Table 2. In the auHSCT study, the percentages of subjects aged 18 years and older reporting each solicited local and general adverse reaction following administration of SHINGRIX (both doses combined) were pain (84%), redness (33%), swelling (19%); fatigue (56%), myalgia (54%), headache (34%), gastrointestinal symptoms (26%), shivering (26%), and fever (20%). In the other 3 studies, the percentages of subjects aged 18 years and older reporting each solicited local and general adverse reaction following administration of SHINGRIX (both doses combined) were pain (80-87%), redness (25-41%), and swelling (12-23%); fatigue (47-70%), myalgia (44-54%), headache (34-41%), gastrointestinal symptoms (18-46%), shivering (22-35%), and fever (16-25%).

Table 2: Percentage of Subjects with Solicited Local and General Adverse Reactions within 7 Days of Vaccination in Adults Aged ≥18 Years following Autologous Hematopoietic Stem Cell Transplant, Renal Transplant, or with Hematologic Malignancies, or with Solid Malignant Tumours (Total Vaccinated Cohort)

	ZOSTER-002		ZOSTER-041		ZOSTER-039		ZOSTER-028	
	Autologous Hematopoietic Stem Cell Transplant		Renal Transplant ^b		Hematologic Malignancies ^c		Solid Malignant Tumours ^d	
	SHINGRIX (%)	Placebo ^e (%)	SHINGRIX (%)	Placebo ^e (%)	SHINGRIX (%)	Placebo ^e (%)	SHINGRIX (%)	Placebo ^e (%)
Local Adverse Reactions	n = 901	n = 892	n = 131	n = 132	n = 278	n = 274	n = 112	n = 110
Pain	84	9	87	8	80	16	80	6
Redness	33	1	25	2	41	2	36	0
Swelling	19	1	12	1	23	1	16	1
General Adverse Reactions	n = 901	n = 894	n = 131	n = 132	n = 278	n = 274	n = 112	n = 110
Myalgia	54	26	50	24	44	18	54	28
Fatigue	56	38	47	40	58	37	70	62
Headache	34	19	34	26	41	23	38	36
Shivering	26	13	22	12	25	7	35	23
Fever ^f	20	6	16	4	25	8	18	5

	ZOSTER-002		ZOSTER-041		ZOSTER-039		ZOSTER-028	
	Autologous Hematopoietic Stem Cell Transplant		Renal Transplant ^b		Hematologic Malignancies ^c		Solid Malignant Tumours ^d	
	SHINGRIX (%)	Placebo ^e (%)	SHINGRIX (%)	Placebo ^e (%)	SHINGRIX (%)	Placebo ^e (%)	SHINGRIX (%)	Placebo ^e (%)
Gastrointestinal ^g	26	21	18	18	27	11	46	45

Total vaccinated cohort for safety included all subjects with at least 1 documented dose (n).

a 7 days included day of vaccination and the subsequent 6 days.

b Renal transplant recipients on chronic immunosuppressive treatment.

c Subjects with hematologic malignancies during a cancer therapy course or after the full cancer therapy course.

d Subjects with solid tumours undergoing chemotherapy.

e Placebo was a sucrose/saline solution.

f Fever defined as $\geq 37.5^{\circ}\text{C}/99.5^{\circ}\text{F}$ for oral, axillary, or tympanic route, or $\geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$ for rectal route.

g GI = Gastrointestinal symptoms including nausea, vomiting, diarrhea, and/or abdominal pain.

In studies with immunocompromised adults aged 18 years and older, there was a higher incidence of pain at the injection site (90% and 82%), fatigue (65% and 56%), myalgia (61% and 50%), headache (49% and 32%), shivering (33% and 25%) and fever (30% and 19%) in subjects aged 18 to 49 years compared with those aged 50 years and older.

Unsolicited Adverse Events

Unsolicited adverse events occurring within 30 days following each vaccination were reported for the total vaccinated cohort in each of the 4 studies: auHSCT, 39% and 38% of subjects who received SHINGRIX or placebo, respectively; renal transplantation, 39% and 33%; hematologic malignancies, 47% and 46%; solid malignant tumours, 86% and 90%. The unsolicited adverse event that occurred in $\geq 1\%$ of recipients of SHINGRIX and at a rate at least 1.5-fold higher than placebo was arthralgia (1.5% versus 1.0%).

Potential Immune-Mediated Diseases

In the 4 studies (auHSCT, renal transplantation, hematologic malignancies, and solid malignant tumours), new onset pIMDs or exacerbation of existing pIMDs were reported for subjects who received SHINGRIX (1.4%, 3%, 1.1%, 0%, respectively) and subjects who received placebo (0.9%, 1.5%, 0.7%, 0.9%, respectively) from the first administered dose up to 1 year post-last vaccination. The most frequently reported pIMDs were comparable in the groups receiving SHINGRIX and the placebo groups.

Use with other vaccines

The incidence of fever and shivering were more frequent when PPV23 was administered with SHINGRIX (16% and 21%, respectively) compared to when SHINGRIX was given alone (7% for both adverse reactions) (study Zoster-035 including 865 adults ≥ 50 years of age).

Post-marketing data

System Organ Class	Frequency	Adverse reactions
Immune system disorders	Rare	hypersensitivity reactions including rash, urticaria, angioedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Insufficient data are available.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Varicella zoster vaccines, ATC code: J07BK03 zoster, purified antigen.

Mechanism of action

By combining the VZV specific antigen (gE) with an adjuvant system (AS01_B), SHINGRIX induces antigen-specific cellular and humoral immune responses in individuals with pre-existing immunity against VZV.

Non-clinical data show that AS01_B induces a local and transient activation of the innate immune system. This facilitates the recruitment and activation of antigen presenting cells carrying gE-derived antigens in the draining lymph node, which in turn leads to the generation of gE-specific CD4+ T cells and antibodies. The adjuvant effect of AS01_B is the result of interactions between MPL and QS-21 formulated in liposomes.

Clinical trials

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 ≥ 50 years with 2 doses administered 2 months apart:

- Zoster-006 (ZOE-50): total vaccinated cohort (TVC) of 15,405 subjects ≥ 50 who received at least one dose of either SHINGRIX (N=7,695) or placebo (N=7,710)
- Zoster-022 (ZOE-70): TVC of 13,900 subjects ≥ 70 who received at least two doses of either SHINGRIX (N=6,950) or placebo (N=6,950).

Two phase III, placebo-controlled, observer-blind studies evaluating Shingrix efficacy were conducted in IC adults ≥ 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) post-transplant.
- 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 or after the full cancer therapy course.

Incidence of HZ and PHN cases as well as vaccine efficacy were evaluated in the modified Total Vaccinated Cohort (mTVC i.e. excluding subjects 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 and PHN compared with placebo in:

- adults ≥ 50 years (Zoster-006): 6 vs. 210 HZ cases and 0 vs. 18 PHN cases;
- adults ≥ 70 years (pooled analysis of Zoster-006 and Zoster-022): 25 vs. 284 HZ cases and 4 vs. 36 PHN cases;
- adults ≥ 18 years with aHSCT (Zoster-002): 49 vs. 135 HZ cases and 1 vs. 9 PHN cases;
- adults ≥ 18 years with hematologic malignancies (Zoster-039): 2 vs. 14 HZ cases (PHN was not assessed as study endpoint). Vaccine efficacy was calculated post-hoc.

Vaccine efficacy results are presented in Table 3 and Table 4, respectively.

Table 3: SHINGRIX efficacy against HZ

Age (years)	SHINGRIX			Placebo			Vaccine efficacy (%) [95% CI]
	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1000 person years	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1000 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

Age (years)	SHINGRIX			Placebo			Vaccine efficacy (%) [95% CI]
	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1000 person years	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1000 person years	
							[80.2; 97.0]
Zoster-002*** (aHSCT recipients#)							
≥ 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#)							
≥ 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.

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 subjects ≥ 50 years (Zoster-006) and subjects ≥ 70 years (pooled Zoster-006 and Zoster-022), 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).

The duration of protection beyond 4 years is currently under investigation.

SHINGRIX significantly decreased the incidence of PHN compared with placebo in subjects ≥50 years (0 vs. 18 cases in ZOE-50) and in subjects ≥ 70 years (4 vs. 36 cases in the pooled analysis of ZOE-50 and ZOE-70).

Table 4: SHINGRIX efficacy against PHN

Age (years)	SHINGRIX			Placebo			Vaccine efficacy (%) [95% CI]
	Number of evaluable subjects	Number of PHN* cases	Incidence rate per 1000 person years	Number of evaluable subjects	Number of PHN cases	Incidence rate per 1000 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[§] [< 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[§] [< 0; 97.1]
Zoster-002**** (aHSCT recipients#)							
≥ 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[§] [< 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. Due to the very low numbers of shingles occurring in the Shingrix group, the efficacy of SHINGRIX in the prevention of PHN in subjects with confirmed HZ could not be demonstrated.

Other HZ-related complications

The evaluated HZ-related complications (other than PHN) were: HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease including stroke, and visceral disease.

In a post-hoc analysis of the pooled data of ZOE-50 and ZOE-70, SHINGRIX reduced HZ-related complications (other than PHN) by 93.7% (95% CI: 59.5; 99.9) and 91.6% (95% CI: 43.3; 99.8) in subjects ≥ 50 years (1 vs. 16 cases) and subjects ≥ 70 years (1 vs. 12 cases), respectively.

In Zoster-002, Shingrix significantly reduced HZ-related complications by 77.8% (95% CI: 19.0; 96.0) in aH SCT recipients ≥ 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).

Reduction of use of pain medication

Among subjects ≥ 70 years with confirmed HZ, SHINGRIX 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.

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 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 at 1 month post-dose 2 are presented in Tables 5 and 6 respectively.

Table 5: Humoral immunogenicity of SHINGRIX in adults ≥ 50 years at 1 month post-dose 2 (ATP cohort for immunogenicity)

Anti-gE immune response [^]				
Age group (years)	N	VRR [§] (%) (95% CI)	GMC (95% CI)	Median fold increase of concentrations vs pre-vaccination (Q1; Q3)
Zoster-006				
≥ 50	1,070	98.5 (97.6; 99.1)	52,376.6 (50,264.1; 54,577.9)	41.9 (20.8; 86.9)
Pooled Zoster-006 and Zoster-022				
≥ 70	742	96.6 (95.1; 97.8)	49,691.5 (47,250.8; 52,258.2)	34.3 (16.7; 68.5)

ATP According-To-Protocol

[^] 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)

[§] Vaccine response rate (VRR) for anti-gE is defined as the percentage of subjects who have at least a 4-fold increase in the post-dose 2 anti-gE antibodies concentration as compared to the pre-vaccination anti-gE antibodies (subjects seropositive at baseline), or as compared to the anti-gE antibodies cut-off value for seropositivity (subjects seronegative at baseline)

CI Confidence interval

GMC Geometric Mean Concentration

Q1; Q3 First and third quartiles

At 3 years post-dose 2, the median fold increase over baseline was 9.3 (Q1: 4.9; Q3: 19.5) in adults ≥ 50 years (Zoster-006) and 7.2 (Q1: 3.5; Q3: 14.5) in adults ≥ 70 years (pooled Zoster-006 and Zoster-022).

Table 6: Cell-mediated immunogenicity of SHINGRIX in adults ≥ 50 years at 1 month post-dose 2 (ATP cohort for immunogenicity)

gE-specific CD4[2+] T cell response [^]			
Age group (years)	N	Median frequency (Q1; Q3)	Median fold increase of frequency vs. pre-vaccination (Q1; Q3)
Zoster-006			
≥ 50	164	1,844.1 (1,253.6; 2,932.3)	24.6 (9.9; 744.2)
$\geq 70^*$	52	1,494.6 (922.9; 2,067.1)	33.2 (10.0; 1,052.0)

ATP According-To-Protocol

[^] 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

Q1; Q3 First and third quartiles

*** The gE-specific CD4[2+] data in the ≥ 70 YOA group were generated in ZOE-50 because CD4+ T cell activity was not assessed in ZOE-70

At 3 years post-dose 2, in Zoster-006, the median fold increase over baseline was 7.9 (Q1: 2.7; Q3: 31.6) in adults ≥ 50 years and 7.3 (Q1: 1.7; Q3: 31.6) in adults ≥ 70 years.

Data from a phase II, open-label, single group, follow-up clinical study in adults ≥ 60 years (Zoster-024) indicate that the vaccine-induced immune response (humoral and CMI) persists up to Month 72 (approximately 6 years post-dose 1 i.e. 70 months post-dose 2), following a 0, 2-month schedule (N= 119).

The median anti-gE antibody concentration was greater than 7-fold above the baseline pre-vaccination median concentration. The median frequency of gE-specific CD4[2+] T cells was greater than 3.7-fold above baseline pre-vaccination median frequency.

In IC adults ≥ 18 years, the humoral and CMI responses to Shingrix were evaluated in:

- one phase I/II study: Zoster-015 (HIV infected subjects);
- one phase II/III study: Zoster-028 (patients with solid tumors 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 at 1 month post-dose 2 in all IC populations studied are presented in Tables 7 and 8, respectively.

Table 7: Humoral immunogenicity of Shingrix in IC adults ≥ 18 years at 1 month post-dose 2 (ATP cohort for immunogenicity)

Anti-gE immune response[^]			
N	VRR[§] (%) (95% CI)	GMC (95% CI)	Median fold increase of concentrations vs pre- vaccination (Q1; Q3)
Zoster-002 (aHSCT recipients)			
82	67.1 (55.8; 77.1)	12,753.2 (7,973.0; 20,399.4)	14.1 (1.7; 137.0)
Zoster-028 (solid tumor patients)			
87	86.2 (77.1; 92.7)	18,291.7 (14,432.1; 23,183.5)	21.5 (7.0; 45.2)
Zoster-039 (hematologic malignancy patients)			
217	65.4 (58.7; 71.7)	13,445.6 (10,158.9; 17,795.6)	17.2 (1.4; 87.4)
Zoster-041 (renal transplant recipients)			
121	80.2 (71.9; 86.9)	19,163.8 (15,041.5; 24,416.0)	15.1 (6.1; 35.0)
Zoster-015 (HIV infected subjects)			
53	98.1 (89.9; 100)	42,723.6 (31,233.0; 58,441.6)	40.9 (18.8; 93.0)

ATP According-To-Protocol

[^] 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)

[§] Vaccine response rate (VRR) for anti-gE is defined as the percentage of subjects who have at least a 4-fold increase in the post-dose 2 anti-gE antibodies concentration as compared to the pre-vaccination anti-gE antibodies (subjects seropositive at baseline), or as compared to the anti-gE antibodies cut-off value for seropositivity (subjects seronegative at baseline)

CI Confidence interval

GMC Geometric Mean Concentration

Q1; Q3 First and third quartiles

Table 8: Cell-mediated immunogenicity of Shingrix in IC adults ≥ 18 years at 1 month post-dose 2 (ATP cohort for immunogenicity)

gE-specific CD4[2+] T cell response[^]		
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)
Zoster-028* (solid tumor patients)		
22	778.8 (393.1; 1,098.2)	4.9 (1.7; 33.0)
Zoster-039 (hematologic malignancy patients)		
53	3,081.9 (1,766.2; 7,413.6)	45.9 (16.4; 2,221.9)
Zoster-041 (renal transplant recipients)		
32	2,149.0 (569.4; 3,695.1)	47.7 (14.7; 439.6)
Zoster-015 (HIV infected subjects)		
41	2,809.7 (1,554.5; 4,663.7)	23.4 (8.5; 604.1)

ATP According-To-Protocol

[^] 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)

In Zoster-028, GMC 1-month post Dose 2 were 22,974.3 (19,080.0; 27663.5) 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.

At 1 year post-dose 2, the median fold increase over baseline ranged from 2.7 to 6.5 in terms of anti-gE antibody concentration and from 2.0 to 43.6 in terms of gE-specific CD4[2+] T-cell frequencies (studies Zoster-002, Zoster-028, Zoster-039 and Zoster-041).

At 2 years post-dose 2, in Zoster-002, the median fold increase over baseline was 1.3 in terms of anti-gE antibody concentration and 50.9 in terms of gE-specific CD4[2+] T-cell frequencies.

Immunogenicity following concomitant vaccination

In three phase III, controlled, open-label clinical studies, adults ≥ 50 years of age were randomized to receive 2 doses of SHINGRIX 2 months apart administered either

concomitantly at the first dose or non-concomitantly with unadjuvanted seasonal influenza vaccine (N=828; Zoster-004), PPV23 vaccine (N=865; Zoster-035) or dTpa vaccine formulated with 0.3 milligrams Al³⁺ (N=830; Zoster-042). The vaccine response rate (in terms of anti-gE antibodies) was 95.8% (95% CI: 93.3; 97.6), 98.3% (95% CI: 96.4; 99.3) and 97.8% (95% CI: 95.8; 99.1) following co-administration of SHINGRIX with the influenza, PPV23 and dTpa vaccine respectively. The immune responses of the co-administered vaccines were unaffected, with the exception of lower geometric mean concentrations (GMCs) for one of the pertussis antigens (pertactin) when SHINGRIX is co-administered with the dTpa vaccine. The clinical relevance of these data is not known.

Immunogenicity in subjects with a history of HZ prior to vaccination

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

Immunogenicity in subjects receiving 2 doses of SHINGRIX 6 months apart

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

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

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

In a phase III, open-label, multicentre clinical study (Zoster-048), 430 adults ≥ 65 years of age with or without a previous history of vaccination with live attenuated HZ vaccine ≥ 5 years earlier were group-matched at a 1:1 ratio to receive 2 doses of SHINGRIX 2 months apart. The immune response to SHINGRIX was unaffected by prior vaccination with live attenuated HZ vaccine. The safety and reactogenicity profiles were comparable in subjects irrespective of previous vaccination with live attenuated HZ vaccine.

5.2 PHARMACOKINETIC PROPERTIES

Not relevant to vaccines.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

SHINGRIX was not tested for genotoxicity.

Carcinogenicity

SHINGRIX was not tested for carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Powder (gE antigen):

Sucrose
Polysorbate 80
Monobasic sodium phosphate dihydrate
Dibasic potassium phosphate

Suspension (AS01_B Adjuvant System):

Dioleoylphosphatidylcholine
Cholesterol
Sodium chloride
Dibasic sodium phosphate
Monobasic potassium phosphate
Water for injections

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

For shelf-life after reconstitution of the medicinal product, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Instructions for Use and Handling.

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 4.2 DOSE AND METHOD OF ADMINISTRATION, Instructions for Use and Handling.

6.5 NATURE AND CONTENTS OF CONTAINER

SHINGRIX is presented as:

- 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 plus 1 vial of suspension or in a pack size of 10 vials of powder plus 10 vials of suspension.

Not all pack sizes and container types may be distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Not relevant to vaccines.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd

Level 4, 436 Johnston Street,

Abbotsford, Victoria, 3067

9 DATE OF FIRST APPROVAL

2 July 2018

10 DATE OF REVISION

9 September 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of potential risk regarding Guillain-Barre syndrome.
4.5, 4.8	New reactogenicity data on coadministration with PPV23 vaccine.

Version 6.0

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