▼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 AS01B2.

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

[2] The GlaxoSmithKline proprietary AS01B 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.

<u>How to prepare SHINGRIX</u>

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.

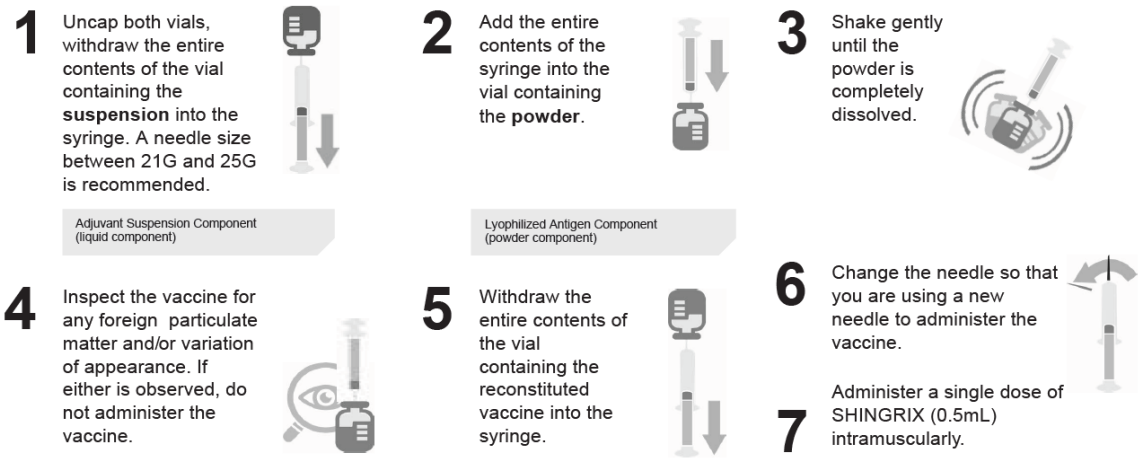
After reconstitution, the vaccine should be used promptly; if this is not possible, the vaccine should be stored in a refrigerator (2°C – 8°C). If not used within 6 hours it should be discarded.

<u>Before administration</u>

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.
3. Administer 0.5mL intramuscularly.

SHINGRIX is for single use in one patient only.

**Figure 1 Reconstitution Instructions**




## 4.3 CONTRAINDICATIONS

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

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

**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.

An increased risk of Guillain-Barré syndrome has been observed following vaccination 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.

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

**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**

The first dose of SHINGRIX can be given concomitantly with either seasonal influenza vaccine (unadjuvanted), 23-valent pneumococcal polysaccharide vaccine (PPV23), pneumococcal conjugate vaccine (PCV), reduced antigen diphtheria-tetanus-acellular pertussis vaccine (dTpa), coronavirus disease 2019 (COVID-19) messenger ribonucleic acid (mRNA) booster vaccine or respiratory syncytial virus (RSV) vaccine (recombinant, adjuvanted) (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). Data are not available for co-administration with the second dose of SHINGRIX. Data are not available for coadministration of SHINGRIX with the primary (100 microgram dose) course of COVID-19 mRNA vaccine. Incidence of arthralgia, chills, fatigue, gastrointestinal symptoms, headache, and myalgia were more frequent when SHINGRIX was co-administered with COVID-19 mRNA-1273 50 micrograms booster vaccine compared to when SHINGRIX was given alone (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

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 AS01B 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 ≥ 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 standardised 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 ≥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** |
| 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 |

| | Aged 50 - 59 Years | | Aged 60 - 69 Years | | Aged ≥70 Years | |
|---|---|---|---|---|---|---|
| | **SHINGRIX %** | **Placebo[c] %** | **SHINGRIX %** | **Placebo[c] %** | **SHINGRIX %** | **Placebo[c] %** |
| 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 ≥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 ≥ 50 years of age 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.

*Long-term follow-up study*

In the long-term follow-up study (follow-up period of approximately 11 years) including more than 7,000 adults ≥ 50 years of age, no new adverse reactions were identified.

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 section 5.1 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[a] 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 Autologous Hematopoietic Stem Cell Transplant | | ZOSTER-041 Renal Transplant[b] | | ZOSTER-039 Hematologic Malignancies[c] | | ZOSTER-028 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 |
| 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 ≥37.5°C/99.5°F for oral, axillary, or tympanic route, or ≥38°C/100.4°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 ≥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).

The incidence of myalgia, fatigue, headache, chills, arthralgia, and gastrointestinal symptoms were more frequent when SHINGRIX was co-administered with a monovalent COVID-19 mRNA-1273 50 micrograms booster (myalgia 64%, fatigue 51.7%, headache 39%, chills 31.5%, arthralgia 30.3%, gastrointestinal symptoms 24%) compared to when SHINGRIX was given alone (myalgia 37.8%, fatigue 32.1%, headache 21.4%, chills 14.9%, arthralgia 19.1%, gastrointestinal symptoms 12.6%) (study Zoster-091 including 539 adults ≥ 50 years of age).

**Post-marketing data**

| **System Organ Class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| Immune system disorders | Rare | hypersensitivity reactions including rash, urticaria, angioedema |
| Nervous system disorders | Rare | vertigo |
| | Very Rare | Guillain-Barré syndrome* |
| General disorders and administration site conditions | Uncommon | injection site induration |

*See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

<u>Post-marketing observational studies of the risk of Guillain-Barré syndrome</u>

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 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 (AS01B), SHINGRIX induces antigen-specific cellular and humoral immune responses in individuals with pre-existing immunity against VZV.

Non-clinical data show that AS01B 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 AS01B 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** [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** |

| 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** | |
| | | | | | | | [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 aHSCT 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).

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 ≥ 50 years from Zoster-006 and Zoster-022. The TVC for efficacy included 7,408 subjects.

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). Estimates of incidence rates in the control group to assess the vaccine efficacy during Zoster-049 study were historical, derived from the Zoster-006 and Zoster-022 placebo groups.

SHINGRIX long-term efficacy results against HZ, PHN and other HZ-related complications up to approximately 11 years post-vaccination are presented in Table 5.

The number of cases of HZ, PHN and other HZ-related complications in subjects who received SHINGRIX compared to controls (see Table 5 for details on controls used) were as follows (age at the time of vaccination):

- Over the duration of Zoster-049:
    - In adults ≥ 50 years: 69 vs. 341 HZ cases, 4 vs. 32 PHN cases, 1 vs. 12 other HZ-related complication cases;
    - In adults ≥ 70 years: 48 vs. 179 HZ cases, 3 vs. 23 PHN cases, 1 vs. 9 other HZ-related complication cases;
- From 1 month post-dose 2 in Zoster-006 and Zoster-022 until the end of Zoster-049:
    - In adults ≥ 50 years: 101 vs. 818 HZ cases, 8 vs. 78 PHN cases, 2 vs. 28 other HZ-related complication cases;
    - In adults ≥ 70 years: 73 vs. 463 HZ cases, 7 vs. 59 PHN cases, 2 vs. 21 other HZ-related complication cases.

**Table 5: Long-term Shingrix efficacy against HZ, PHN and HZ-related complications other than PHN (mTVC)**

| Age at the time of vaccination (years) | HZ | | | PHN | | | HZ-related complications other than PHN | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Efficacy* (%) | 95% CI | N | Efficacy* (%) | 95% CI | N | Efficacy* (%) | 95% CI |
| **Over the duration of Zoster-049** | | | | | | | | | |
| ≥ 50 | 7,258 | 79.8 | 73.7; 84.6 | 7,271 | 87.5 | 64.8; 96.8 | 7,273 | 91.7 | 43.7; 99.8 |
| ≥ 70 | 3,973 | 73.2 | 62.9; 80.9 | 3,982 | 87.0 | 56.8; 97.5 | 3,984 | 88.9 | 19.8; 99.8 |
| **From 1 month post-dose 2 in Zoster-006/Zoster-022 until the end of Zoster-049** | | | | | | | | | |
| ≥ 50 | 13,881 | 87.7 | 84.9; 90.1 | 13,881 | 89.7 | 78.7; 95.7 | 13,881 | 92.8 | 71.6; 99.2 |
| ≥ 70 | 8,250 | 84.3 | 79.9; 87.9 | 8,250 | 88.1 | 73.9; 95.4 | 8,250 | 90.5 | 60.9; 98.9 |

N Number of evaluable subjects
CI Confidence interval
* Descriptive efficacy analysis
Zoster-049 mTVC: N (Shingrix) = 7,258 (HZ), 7,271 (PHN), 7,273 (other HZ-related complications). The same N were assumed for the corresponding historical control groups.
Zoster-049 mTVC started at a median of 5.6 years post-vaccination in Zoster-006/022 and ended at a median of 11.4 years post-vaccination.
Zoster-006 / 022 / 049 mTVC: N (Shingrix) = 13,881, N (Placebo / Historical control) = 14,035. Placebo group in Zoster-006 / 022 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.

In the eleventh year after vaccination, the efficacy against HZ was 82.0% (95% CI: 63.0; 92.2) and 72.0% (95% CI: 33.4; 89.8) in subjects ≥ 50 years (SHINGRIX group: N=5,849) and subjects ≥ 70 years (SHINGRIX group: N=2,891), 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), received 2 doses of either SHINGRIX or placebo 2 months apart. The Exposed Set (ES) included 1426 subjects who received at least one dose of either SHINGRIX (N = 714) or placebo (N = 712). A total of 1286 subjects in the ES 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 i.e., excluding subjects who did not receive the second dose of vaccine or who had a confirmed diagnosis of HZ within 30 days after the second dose). The mES included 1350 subjects [N = 668 (SHINGRIX), N=682 (placebo)].

In subjects with a prior history of HZ, Shingrix vaccination did not increase the recurrence of HZ (0 HZ cases in the SHINGRIX group vs. 8 HZ cases in the placebo group). The incidence rate ratio of HZ recurrence (SHINGRIX vs. placebo) in the mES from 30 days post-dose 2 until end of Zoster-062 was 0.00 (95% CI: 0.00; 0.46).

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 6 and 7 respectively.

**Table 6: 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 7: 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) |
| **≥ 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.

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 8 and 9, respectively.

**Table 8: 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 9: 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 six 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 seasonal influenza vaccine (unadjuvanted) (N=828; Zoster-004); PPV23 vaccine (N=865; Zoster-035); PCV13 vaccine (N=912; Zoster-059); dTpa vaccine formulated with 0.3 milligrams $Al^{3+}$ (N=830; Zoster-042); monovalent COVID-19 mRNA-1273 50 micrograms booster vaccine (Original SARS-CoV-2 strain) (N=458; Zoster-091); or RSV vaccine (recombinant, adjuvanted) (N=530; RSV OA=ADJ-020). The vaccine response rates (in terms of anti-gE antibodies) were 95.8% (95% CI: 93.3; 97.6), 98.3% (95% CI: 96.4; 99.3), 99.1% (95% CI: 97.6; 99.7) 97.8% (95% CI: 95.8; 99.1), 97.4% (95% CI: 94.4; 99.0) and 92.9% (95% CI: 88.4; 96.1) following co-administration of SHINGRIX with the influenza (unadjuvanted), PPV23, PCV13, dTpa, COVID-19 mRNA-1273 booster and RSV (recombinant, adjuvanted) vaccines 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 adults ≥ 50 years with a prior history of HZ (resolved > 6 months prior to enrolment), the immune responses to SHINGRIX were evaluated in subjects from the phase III study Zoster-062. The gE-specific immune responses (humoral) elicited by SHINGRIX at 30 days post-dose 2 are presented in Table 10.

**Table 10: Humoral immunogenicity of SHINGRIX in adults ≥ 50 years, with a prior history of HZ, at 30 days post-dose 2 (PPS cohort for immunogenicity)**

| **Anti-gE immune response^** | | | |
|---|---|---|---|
| **N** | **VRR§ (%) (95% CI)** | **GMC (95% CI)** | **Median fold increase of concentrations vs pre-vaccination (Q1; Q3)** |
| 534 | 95.3 (93.1; 96.9) | 49175.8 (46500.4; 52005.1) | 24.4 (11.9; 47.5) |

PPS Per Protocol Set
^ 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

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.

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 ≥ 50 years from Zoster-006 and Zoster-022. At Year 12 post-vaccination, MGI (Mean Geometric Increase versus pre-vaccination) of anti-gE antibody concentrations in 435 evaluable subjects was 5.8 (95% CI: 5.2; 6.4). 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 ≥ 18 years on chronic immunosuppressive therapy from Zoster-041. Zoster-073 study started 4 to 6 years post-vaccination in Zoster-041. At Month 24 (approximately 6 to 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 (MGI). Median frequency of gE specific CD4[2+] T cells at Month 24 in 19 evaluable subjects in CMI subset remained above pre-vaccination level.

## 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 (AS01B 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

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## 9 DATE OF FIRST APPROVAL

2 July 2018

## 10 DATE OF REVISION

29 October 2026

**SUMMARY TABLE OF CHANGES**

| Section Changed | Summary of new information |
|---|---|
| **4.2** | Addition of Figure 1, Reconstitution Instructions |
| **4.4** | Addition of indication warning |

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