Summary Report of Benefit-Risk Assessment

SHINGRIX POWDER AND SUSPENSION FOR SUSPENSION FOR INJECTION 50MCG/0.5ML

NEW DRUG APPLICATION

Active Ingredient(s)	[Antigen] Recombinant Varicella Zoster Virus glycoprotein E (gE)
Product Registrant	Glaxosmithkline Pte Ltd
Product Registration Number	SIN16079P
Application Route	Abridged evaluation
Date of Approval	12 Jan 2021

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A INTRODUCTION

Shingrix is indicated for the prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in adults 50 years of age or older. The vaccine's effect on the prevention of PHN can be attributed to the effect of the vaccine on the prevention of HZ. The use of Shingrix should be based on official recommendations.

Shingrix is presented as a powder and suspension for suspension for injection, containing 50 micrograms of glycoprotein E (gE) antigen (powder) adjuvanted with $AS01_B$ (suspension). Varicella Zoster Virus (VZV) gE is produced by recombinant DNA technology in Chinese Hamster Ovarian cells. The $AS01_B$ adjuvant system contains the following immunoenhancers QS-21 (Quillaria saponaria Molina, fraction 21) and monophosphoryl lipid A (MPL A), combined with liposomes. These and all other excipients are listed below:
Other ingredients:
Powder (gE antigen): sucrose, polysorbate 80, sodium dihydrogen phosphate dihydrate, dipotassium phosphate
Suspension ($AS01_B$ adjuvant system): dioleoyl phosphatidylcholine, cholesterol, sodium chloride, disodium phosphate anhydrous, potassium dihydrogen phosphate, water for injections.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, recombinant Varicella Zoster Virus glycoprotein E (gE), is manufactured at [redacted]. The drug product, Shingrix Powder and Suspension for Suspension for Injection 50mcg/0.5mL, consisting of both the antigen and adjuvant vials, are also manufactured at [redacted].

Drug substance:
Adequate controls have been presented for the starting materials, intermediates, reagents, and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented for [redacted] were adequate to support the approved storage condition and shelf life period. The packaging is [redacted]. The drug substance is approved for storage at [redacted] with a shelf life of [redacted].

Drug product:

The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, content and potency testing is presented.

For both the antigen and adjuvant, the stability data submitted were adequate to support the approved shelf-life of 36 months when stored between 2ºC and 8ºC. The container closure system for both the antigen and adjuvant are [redacted] Type 1 glass vials with rubber stoppers and aluminium caps. The in-use period after reconstitution is 6 hours and this is supported with appropriate data.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of Shingrix for the prevention of HZ and PHN in adults 50 years of age or older was based on two pivotal studies (ZOSTER-006 and ZOSTER-022).

Studies ZOSTER-006 and -022 were phase III, randomised, observer-blind, placebo-controlled (Normal saline), multicentre trials to assess the prophylactic efficacy, safety, and immunogenicity of gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years of age and older (≥ 50YOA, Study ZOSTER-006) or adults aged 70 years and older (≥ 70YOA, Study ZOSTER-022).

In both studies, the primary efficacy endpoint was confirmed HZ cases during the study in the modified total vaccinated cohort (mTVC). Secondary endpoints included the detection of PHN, HZ-related complications (other than PHN), mortality and hospitalisations, and use of pain medication. A pre-specified vaccine efficacy (VE) analysis was performed on pooled ZOSTER-006 and ZOSTER-022 efficacy data in ≥70 YOA at the time both studies were completed. The co-primary endpoints of this analysis were to evaluate VE in the prevention of overall PHN and VE estimation in the prevention of HZ compared to placebo in subjects ≥70 YOA across both Phase III studies. The studies were not powered to demonstrate VE against PHN in subjects with a confirmed case of HZ.

The pre-planned null-hypotheses to be tested was HZ VE ≤ 25% for all patients in mTVC in study ZOSTER-006. The efficacy in the age strata 50-59, 60-69 was demonstrated if the lower bound of the 95% CI of VE was above 10%. In study ZOSTER-022, the null-hypotheses was to test HZ VE ≤ 10% for all patients in mTVC. If above hypotheses were rejected the following (null-) hypotheses were to be tested in the pooled data set of Study ZOSTER-006 and -022: PHN VE ≤ 0% for all patients ≥ 70 years of age; PHN VE ≤ 0% for all patients; PHN VE ≤ 0% for all patients with confirmed HZ and $HR_{\text{time to cessation of worst pain}}$ ≥ 1 for all patients ≥ 70 years of age.

In study ZOSTER-006, a total of 16,145 subjects were randomised in a 1:1 ratio to the Shingrix group (N=8068) or to the placebo Group (N=8077). Of which, 14,759 were included in the mTVC for the final efficacy analysis (7344 in the Shingrix vaccine group and 7415 in the placebo group). The demographic characteristics were similar between the two study groups and within main age strata. The mean age at enrolment was 62.3 years, with a distribution of 47.3%, 29.1%, and 23.6% of participants at 50-59 YOA, 60-69 YOA, and ≥ 70 YOA, respectively. Most participants were female (61.2%) and Caucasians (71.8%) and were enrolled from Europe (51.6%).

In study ZOSTER-022, a total of 13,163 subjects were part of the mTVC group. The mean age of participants at enrolment in the mTVC was 75.5 YOA (range: 62-96 YOA); 45.3% of the subjects were male and 54.7% female. The population was predominantly of Caucasian/ European Heritage (77.0%) with 12.7% being of Asian-East Asian Heritage.

Shingrix demonstrated superiority in preventing HZ in subjects aged ≥ 50 and ≥ 70 YOA with a VE of 97.16% (95% CI: 93.72, 98.97) and 89.79% (84.29, 93.66) in studies ZOSTER-006 and -002, respectively. The protection after vaccination was maintained over 4 years and was consistent across age groups of 50 to 59, 60 to 69 and ≥ 70 YOA. VE in the prevention of PHN was also demonstrated in the pooled analyses, with 91.22% (75.95, 97.70) and 88.78% (68.70, 97.10) in subjects above ≥ 50 and ≥ 70 YOA, respectively. Although, superiority was demonstrated in the prevention of PHN in the overall population, in the subgroup of subjects with confirmed HZ episodes, no significant benefit in the reduction of PHN was seen when compared to placebo (12.50% [4/32] vs 9.64% [46/477] for Shingrix vs placebo). However, this could be due to the low number of confirmed HZ cases in the Shingrix arm due to the high VE of prevention of HZ. The vaccine's effect on the prevention of PHN could be attributed to the effect of the vaccine on the prevention of HZ.

VE in the prevention of HZ

		Incidence rate*		VE	
Study	**Age strata**	**Shingrix**	**Placebo**	**% (95% CI)**	**p-value**
006**	≥ 50 YOA	0.3 (6/ 7344)	9.1 (210/ 7415)	97.16 (93.72, 98.97)	<0.0001
	50-59 YOA	0.3 (3/ 3492)	7.8 (87/ 3525)	96.57 (89.62, 99.31)	<0.0001
	60-69 YOA	0.3 (2/ 2141)	10.8 (75/ 2166)	97.36 (90.14, 99.69)	<0.0001
	≥ 60 YOA	0.2 (3/ 3852)	10.2 (123/ 3890)	97.58 (92.77, 99.51)	<0.0001
	≥ 70 YOA	0.2 (1/ 1711)	9.0 (48/ 1724)	97.93 (87.91, 99.95)	<0.0001
	≥ 80 YOA	0 (0/ 355)	11.4 (14/ 359)	100.0 (70.60, 100.0)	0.0001
022***	≥ 70 YOA	0.9 (23/ 6541)	9.2 (223/ 6622)	89.79 (84.29, 93.66)	<0.0001
	70-79 YOA	0.9 (17/ 5114)	8.8 (169/ 5189)	90.02 (83.54, 94.32)	<0.0001
	≥ 80 YOA	1.2 (6/ 1427)	11 (54/ 1433)	89.08 (74.65, 96.16)	<0.0001
Pooled	≥ 70 YOA	0.8 (25/ 8250)	9.3 (284/ 8346)	91.30 (86.88, 94.46)	<0.0001
	70-79 YOA	0.8 (19/ 6468)	8.9 (216/ 6554)	91.27 (86.04, 94.85)	<0.0001
	≥ 80 YOA	1.0 (6/ 1782)	11.1 (68/ 1792)	91.37 (80.22, 96.94)	<0.0001

*: per 1000 person-years (n/N)
**: Results based on mTVC, final HZ efficacy analysis.
***: Results based on mTVC, EOS analysis.

VE in the prevention of overall PHN

		Incidence rate*		VE	
Study	**Age strata**	**Shingrix**	**Placebo**	**% (95% CI)**	**p-value**
006**	≥ 50 YOA	0 (0/ 7340)	0.6 (18/ 7413)	100.0 (77.11, 100.0)	<0.0001
	50-59 YOA	0 (0/ 3491)	0.6 (8/ 3523)	100.0 (40.88, 100.0)	0.0081
	60-69 YOA	0 (0/ 2140)	0.2 (2/ 2166)	100.0 (-442.83, 100.0)	0.5097
	≥ 60 YOA	0 (0/ 3849)	0.7 (10/ 3890)	100.0 (55.25, 100.0)	0.0020
	≥ 70 YOA	0 (0/ 1709)	1.3 (8/ 1724)	100.0 (41.40, 100.0)	0.0078
	≥ 80 YOA	0 (0/ 355)	0.8 (1/ 359)	100.0 (-3864.04, 100.0)	1.0000
022***	≥ 70 YOA	0.2 (4/ 6541)	1.1 (28/ 6622)	85.49 (58.52, 96.30)	<0.0001
	70-79 YOA	0.1 (2/ 5114)	1.1 (22/ 5189)	90.80 (62.57, 98.95)	<0.0001
	≥ 80 YOA	0.4 (2/ 1427)	1.2 (6/ 1433)	65.76 (-91.58, 96.62)	0.3072
Pooled	≥ 50 YOA	0.1 (4/ 13881)	0.9 (46/ 14035)	91.22 (75.95, 97.70)	<0.0001

70-79 YOA	0.1 (2/ 6468)	1.2 (29/ 6554)	93.04 (72.47, 99.19)	<0.0001
≥ 70 YOA	0.1 (4/ 8250)	1.2 (36/ 8346)	88.78 (68.70, 97.10)	<0.0001
≥ 80 YOA	0.3 (2/ 1782)	1.1 (7/ 1792)	71.16 (-51.51, 97.08)	0.1844

*: per 1000 person-years (n/N)
**: Results based on mTVC, EOS analysis. The study was not powered for this analysis.
***: Results based on mTVC, EOS analysis. The study was not powered for this analysis.

In post-hoc analysis, complications related to HZ (other than PHN) were reported for 1 subject (1 complication) in the vaccine group and 16 subjects (17 complications) in the placebo group (Pooled analysis, ≥ 50 YOA). The HZ related complications (other than PHN) reported during the entire study period in the vaccine group were ophthalmic disease (n=1), and those reported in the placebo group were ophthalmic disease (n=7), disseminated disease (n=6), neurological disease (n=3) and HZ vasculitis (n=1). No cases of visceral disease or stroke were reported during these studies in either groups.

Immunogenicity data from a subset of subjects in Study ZOSTER-006 showed a strong anti-gE antibody response with the mean geometric increase (MGI) of 42.0 [95%CI: 39.3, 44.8] at Month 3 and remained higher than pre vaccination levels with a MGI of 9.7 [95%CI: 9.1, 10.4] at Month 38. The gE-specific CD4 cell mediated immunity response (CMI) showed a pattern similar to the anti-gE humoral immunogenicity results. Data was consistent across age groups and study regions.

A 0- and 6-month vaccination schedule was non-inferior to the 0- and 2-month schedule based on humoral immune response. Shingrix induced strong immune responses in subjects ≥65 YOA who had been vaccinated with Zostavax ≥ 5 years (Prev-Zvax). The immunogenicity primary objective evaluating non-inferiority of Prev-Zvax compared to no Prev-Zvax for humoral immune response at 1-month post Dose 2 was met, as the adjusted geometric mean concentration (GMC) ratio was 1.04 with an upper limit of 1.17 (statistical criterion: <1.5). Results from descriptive analyses of humoral and CMI immune responses at various timepoints show no apparent differences in seropositivity rates, GMCs of anti-gE antibodies and CMI responses between groups.

Overall, the pivotal studies ZOSTER-006 and -022 demonstrated high VE against HZ (97.16% and 89.79%) and PHN (91.22% and 88.78%) in subjects ≥ 50 and ≥ 70 YOA. In the subgroup of subjects ≥ 50 YOA with confirmed HZ episode, no benefit was seen (PHN incidence was 12.50% [4/32] vs 9.64% [46/477] for Shingrix vs placebo), which might be due to the low number of confirmed HZ cases due to high VE of Shingrix against HZ. The vaccine's effect on the prevention of PHN could be attributed to the effect of the vaccine on the overall prevention of HZ. A 0- and 6-month vaccination schedule was non-inferior to the 0- and 2-month schedule based on humoral immune response. In another study, Shingrix induced strong immune responses in subjects ≥65 YOA who had been vaccinated with Zostavax ≥5 years.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of Shingrix was based primarily on safety data derived from the pivotal studies ZOSTER-006 and -022, comprising a total of 14,645 in the Shingrix group and 14,660 in the placebo group. The median duration of treatment was 4.1 (0 - 4.5) years and 3.9 (0- 4.5) years for studies ZOSTER-006 and -022 respectively.

Overview of safety profile (Study ZOSTER-006 and -022)

AE	Shingrix (N=14,645)	Placebo (N=14,660)
At least 1 solicited AE (≥ 50YOA)	84.5%	33.7%

50-69 YOA/ ≥ 70 YOA	89.6%/ 78.7%	38.1%/ 28.7%
Solicited local symptoms	80.8%	11.7%
Solicited general symptoms	64.8%	29.1%
Unsolicited AEs	50.5%	32.0%
SAE	1,880 (12.8%)	1,945 (13.3%)
Treatment-related SAE	15 (0.1%)	15 (0.1%)
Discontinuations due to AE	116 (0.79%)	65 (0.44%)
Deaths due to SAE	634 (4.3%)	680 (4.6%)
Deaths due to SAE related* to treatment	1 (0.007%)	0 (0)

*as determined by the investigator

At least one solicited symptom (local or general) during the 7-day post-vaccination period was experienced by 84.5% of subjects in the Shingrix group and 33.7% of subjects in the placebo group. Local and systemic reactogenicity was higher in the Shingrix (80.8% and 64.8%) versus placebo groups (11.7%, 29.1%). The most common solicited adverse events (AEs) were pain (68.1%), redness (27.8%), swelling (18.0%) and solicited systemic symptom AEs were myalgia (32.9%), fatigue (32.2%) and headache (26.3%). Other common symptoms were GI disorders including nausea, vomiting, diarrhoea and/or abdominal pain (10.7%), shivering (17.6%) and fever (12.8%). The solicited local and general symptoms were mostly mild to moderate in intensity.

Overall, reactogenicity was not observed to increase with the second dose, and was slightly lower in the older age group (i.e. ≥70 years of age) compared with the younger one (50 to 69 years of age). SAEs, including fatal cases, were equally distributed between Shingrix group and Placebo, with a frequency of ~13% for all SAEs and 0.1% for related SAEs (as per investigator assessment) in each group. Majority of SAEs, including fatal cases, occurred in ≥70 YOA and with time to onset longer than one year after last vaccination. These included 634 subjects (4.3%) in the Shingrix group and 680 subjects (4.6%) in the placebo group reported onset of SAEs with fatal outcome. Only one fatal SAE of neutropenic sepsis was considered causally related to vaccination by the investigator. The drop-out rate due to (S)AEs was low and balanced between the Shingrix and Placebo groups.

Adverse events of clinical importance, potentially immune mediated diseases (pIMDs), were equally distributed between Shingrix group and placebo, with a frequency of ~1% for all pIMDs and 0.1% for related pIMDs (as per investigator assessment) in each group. The most frequently reported pIMDs in both groups were polymyalgia rheumatica, rheumatoid arthritis, psoriasis and autoimmune thyroiditis. The incidence of pIMDs was balanced between age groups, and about half of the pIMDs occurred with time to onset longer than one year after last vaccination.

The safety and reactogenicity profiles were within the same range in study subjects irrespective of previous vaccination with Zostavax.

Overall, Shingrix presented an acceptable safety profile and appropriate warnings and precautions have been included in the package insert to address the identified adverse events.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The currently authorised HZ vaccine demonstrated moderate efficacy against HZ which further reduced in ≥70 YOA. In addition, the live attenuated vaccine is contra-indicated in adults with immunosuppression or immunodeficiency due to the risk of vaccine-associated rash or

disseminated disease. Shingrix presents a favourable alternative that has higher vaccine efficacy and can be used in a broader target population.

In the pivotal study ZOSTER-006 and -022, overall high VE against HZ (97.16% and 89.79%) and PHN (91.22% and 88.78%) had been demonstrated in subjects ≥ 50 and ≥ 70 YOA. In the subgroup of subjects ≥ 50 YOA with confirmed HZ episode, no benefit was seen (PHN incidence was 12.50% [4/32] vs 9.64% [46/477] for Shingrix vs placebo), which might due to the low number of confirmed HZ cases with a high VE against HZ. The vaccine's effect on the prevention of PHN could be attributed to the effect of the vaccine on the prevention of HZ.

The safety profile was mainly characterised by reactogenicity events. The incidence of these events was lower in the older age group compared to the younger subjects. The solicited local and systemic symptoms were mostly mild to moderate in intensity with a median duration of 2-3 days. There was no imbalance in SAEs and deaths between the Shingrix group and Placebo group. One fatal SAE of neutropenic sepsis was considered causally related to the vaccination by the investigator. Based on the age of the subject (90-year old male), the long time to onset (97 days after first vaccination), as well as the potential contribution of the concomitant acazitidine treatment for acute myeloid leukemia which the subject developed 75 days after first vaccination, a causal-relationship with the vaccination is unlikely. Overall, there were no significant safety concerns and the AEs were considered manageable.

Taken together, the benefit-risk profile of Shingrix for the prevention of HZ and PHN in adults 50 years of age or older, was considered favourable. The vaccine's effect on the prevention of PHN can be attributed to the effect of the vaccine on the prevention of HZ.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Shingrix for the prevention of HZ and PHN in adults 50 years of age or older was deemed favourable and approval of the product registration was granted on 12 Jan 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

Shingrix

Herpes zoster (HZ, or shingles) vaccine (non-live recombinant, $AS01_B$ adjuvanted)

QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 ml) contains 50 micrograms of gE antigen[1] adjuvanted with $AS01_B$[2].

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

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

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

PHARMACEUTICAL FORM

Powder and suspension for suspension for injection.

CLINICAL PARTICULARS

Indications

Shingrix is indicated for the prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in adults 50 years of age or older (see *Pharmacodynamics*).

The vaccine's effect on the prevention of PHN can be attributed to the effect of the vaccine on the prevention of HZ.

The use of *Shingrix* should be based on official recommendations.

Dosage and Administration

The immunisation schedules for *Shingrix* should be based on official recommendations.

Posology

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.

The need for booster doses has not been established.

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

Shingrix is not indicated for prevention of primary varicella infection.

Method of administration

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

For instructions on reconstitution of the medicinal product before administration, see *Instructions for Use/Handling*.

Contraindications

Hypersensitivity to the active substances or to any component of the vaccine (see *Qualitative and Quantitative Composition* and *Excipients*).

Warnings and Precautions

Prior to immunisation

It is good clinical practice to precede vaccination by a review of the medical history (especially with regards 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.

Precautions for use

Do not administer the vaccine intravascularly, intradermally or subcutaneously.

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

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

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

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

Systemic immunosuppressive medications and immunodeficiency

There are limited data available on the use of *Shingrix* in immunocompromised adults ≥ 50 years old.

Interactions

Use with other vaccines

Shingrix can be given concomitantly with unadjuvanted seasonal influenza vaccine, 23-valent pneumococcal polysaccharide vaccine (PPV23) or reduced antigen diphtheria-tetanus-acellular pertussis vaccine (dTpa) (see *Pharmacodynamic Effects* and *Adverse Reactions*).

If *Shingrix* is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

Pregnancy and Lactation

Fertility

Animal studies indicate no effects of *Shingrix* on male or female fertility.

Pregnancy

There are no data on the use of *Shingrix* in pregnant women. Animal studies performed with *Shingrix* administered to female rats do not indicate any harmful effects with respect to pregnancy (see *Non-clinical information*).

Lactation

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

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.

Adverse Reactions

Clinical trial data

Summary of the safety profile

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

The incidence of adverse reactions was higher in subjects aged 50-69 years compared to those aged ≥70 years, especially for general adverse reactions such as myalgia, fatigue, headache, shivering, fever and gastrointestinal symptoms.

Safety in subjects vaccinated following a 0, 6-month schedule

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.

Safety 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 an unadjuvanted inactivated seasonal influenza vaccine (N=828; Zoster-004), a PPV23 vaccine (N=865; Zoster-035) or a dTpa vaccine formulated with 0.3 milligrams Al^{3+} (N=830; Zoster-042).

The safety and reactogenicity profiles were comparable irrespective of whether the subjects received *Shingrix* alone or *Shingrix* co-administered with either dTpa or influenza vaccines. In study Zoster-035, the adverse reactions of fever and shivering were more frequent when PPV23 vaccine is co-administered with *Shingrix*.

Safety in subjects with Previous History of Vaccination with Live Attenuated HZ Vaccine

In a phase III clinical study Zoster-048, where 430 adults ≥ 65 years of age with or without a previous history of vaccination with live attenuated HZ vaccine were vaccinated with at least 1 dose of *Shingrix*, the safety and reactogenicity profiles were comparable in subjects irrespective of previous vaccination with live attenuated HZ vaccine.

Tabulated list of adverse reactions

The safety profile presented below is based on a pooled analysis of more than 14,500 adults ≥ 50 years of age, who have received at least one dose of *Shingrix*. These data were generated in placebo-controlled clinical studies (conducted in Europe, North America, Latin America, Asia and Australia) where *Shingrix* was administered according to a 0, 2-month schedule.

Adverse reactions reported are listed according to the following frequency:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000

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

[1] Adverse reactions from spontaneous reporting

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.

Post-marketing data

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

Overdose

Insufficient data are available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

Pharmacotherapeutic group: Varicella zoster vaccines, ATC code: J07BK.

Mechanism of Action

Shingrix is designed to induce antigen-specific cellular and humoral immune responses in individuals with pre-existing immunity against VZV.

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

Pharmacodynamic Effects

1. Efficacy of *Shingrix*

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

In two phase III, placebo-controlled, observer-blind efficacy studies of *Shingrix*, Zoster-006 (ZOE-50) and Zoster-022 (ZOE-70), respectively:
- 15,405 subjects ≥ 50 years were randomised to receive two doses of either *Shingrix* (N=7,695) or placebo (N=7,710) administered 2 months apart.
- 13,900 subjects ≥ 70 years were randomised to receive two doses of either *Shingrix* (N=6,950) or placebo (N=6,950) administered 2 months apart.

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

Efficacy results observed 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, are presented in Table 1 and Table 2, respectively.

Shingrix significantly decreased the incidence of HZ compared with placebo in subjects ≥ 50 years (6 vs. 210 cases in Zoster 006) and in subjects ≥ 70 years (25 vs. 284 cases in the pooled analysis of Zoster-006 and Zoster-022).

Table 1: *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	
Zoster-006*							
≥ 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 Zoster-006 and Zoster-022**							
≥ 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]

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 Zoster-006 and Zoster-022 (mTVC) as these analyses provide the most robust estimates for vaccine efficacy in this age group.

Shingrix significantly decreased the incidence of PHN compared with placebo in subjects ≥ 50 years (0 vs. 18 cases in Zoster 006) and in subjects ≥ 70 years (4 vs. 36 cases in the pooled analysis of Zoster-006 and Zoster-022).

Table 2: *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**	
Zoster-006**							
≥ 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 Zoster-006 and Zoster-022***							
≥ 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]

* 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 Zoster-006 and Zoster-022 (mTVC) as these analyses provide the most robust estimates for vaccine efficacy in this age group.
§ Not statistically significant.

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

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

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

Efficacy against other HZ-related complications

In the pooled analysis of Zoster-006 and Zoster-022, *Shingrix* significantly 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. The evaluated HZ-related complications were: HZ vasculitis, disseminated

disease, ophthalmic disease, neurologic disease, visceral disease and stroke. No cases of visceral disease or stroke were reported during these studies.

Effect of Shingrix on HZ-associated pain

In Zoster-022, *Shingrix* significantly reduced the use and the duration of HZ-associated pain medication by 39.6% (95% CI: 10.7; 64.8) and 49.3% (95% CI: 2.9; 73.5), respectively, in subjects ≥ 70 years with at least one confirmed HZ episode. The median duration of pain medication use was 30.0 and 38.0 days in the *Shingrix* and placebo group, respectively.

Overall there was a general trend towards less severe HZ-associated pain in subjects vaccinated with *Shingrix* compared to placebo.

2. 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.

The immune responses to *Shingrix* were evaluated in a subset of subjects from the phase III efficacy studies Zoster-006 [humoral immunity and cell-mediated immunity (CMI)] and Zoster-022 (humoral immunity)]. *Shingrix* elicited higher gE-specific immune responses (humoral and CMI) at 1 month post-dose 2 when compared to pre-vaccination levels.

In Zoster-006 and Zoster-022, the immunogenicity of *Shingrix* was evaluated up to Month 38 (3 years post-dose 2).
The humoral immunogenicity and CMI results are presented in Tables 2 and 3, respectively.

Table 2: Humoral immunogenicity of *Shingrix* in adults ≥ 50 years (ATP cohort for immunogenicity)

Anti-gE immune response^							
Age group (years)	Month 3*				Month 38**		
	N	VRR§ (%) (95% CI)	GMC (95% CI)	Median fold increase of concentrations vs pre-vaccination (Q1; Q3)	N	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)	967	11,919.6 (11,345.6; 12,522.7)	9.3 (4.9; 19.5)
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)	648	10,507.7 (9,899.2; 11,153.6)	7.2 (3.5; 14.5)

ATP According-To-Protocol
^ Anti-gE immune response = anti-gE antibody levels, measured by anti-gE enzyme-linked immunosorbent assay (gE ELISA)
* Month 3 = 1 month post-dose 2
** Month 38 = 3 years post-dose 2
N Number of evaluable subjects at the specified time point (for the GMC)

§ 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 3: Cell-mediated immunogenicity of *Shingrix* in adults ≥ 50 years (ATP cohort for immunogenicity)

gE-specific CD4[2+] T cell response^						
Age group (years)	Month 3*			Month 38**		
	N	Median frequency (Q1; Q3)	Median fold increase of frequency vs. pre-vaccination (Q1; Q3)	N	Median frequency (Q1; Q3)	Median fold increase of frequency vs. pre-vaccination (Q1; Q3)
Zoster-006						
≥ 50	164	1,844.1 (1,253.6; 2,932.3)	24.6 (9.9; 744.2)	152	738.9 (355.7; 1,206.5)	7.9 (2.7; 31.6)
≥ 70* **	52	1,494.6 (922.9; 2,067.1)	33.2 (10.0; 1,052.0)	46	480.2 (196.1; 972.4)	7.3 (1.7; 31.6)

ATP According-To-Protocol
^ gE-specific CD4[2+] T cell response = gE-specific CD4+ T cell activity, measured by intracellular cytokine staining (ICS) assay (CD4[2+] T cells = CD4+ T cells expressing at least 2 of 4 selected immune markers)
* Month 3 = 1 month post-dose 2
** Month 38 = 3 years post-dose 2
N Number of evaluable subjects at the specified time point
Q1; Q3 First and third quartiles
*** The gE-specific CD4[2+] data in the ≥70 YOA group were generated in Zoster-006 because CD4+ T cell activity was not assessed in Zoster-022

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.

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 Al^{3+} (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. However, these data do not suggest clinically relevant interference.

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 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.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical studies

See *Pharmacodynamic Effects*.

NON-CLINICAL INFORMATION

Reproductive Toxicology

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

Animal toxicology and/or pharmacology

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

PHARMACEUTICAL PARTICULARS

List of Excipients

Powder (gE antigen):

Sucrose
Polysorbate 80
Sodium dihydrogen phosphate dihydrate
Dipotassium phosphate

Suspension ($AS01_B$ Adjuvant System):

Dioleoyl phosphatidylcholine
Cholesterol
Sodium chloride
Disodium phosphate anhydrous
Potassium dihydrogen phosphate
Water for injections

Shelf Life

3 years

For shelf-life after reconstitution of the medicinal product, see *Instructions for Use/Handling*.

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 *Instructions for Use/Handling*.

Nature and Contents of Container

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

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

Not all pack sizes may be available.

Incompatibilities

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

Instructions for Use/Handling

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

How to prepare *Shingrix*:

Shingrix must be reconstituted prior to administration.

1. Withdraw the entire contents of the vial containing the suspension into 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.

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

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Product Registrant:
GlaxoSmithKline Pte Ltd, 23 Rochester Park, Singapore 139234

[GSK Logo]