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 Ovary (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;
- adults 18 years of age or older at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy.

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 schedule 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.

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

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.

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

Precautions for use

Do not administer the vaccine intravascularly, intradermally or subcutaneously.

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

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

Syncope (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. Healthcare professionals therefore need to weigh the benefits and risks of HZ vaccination on an individual basis.

Interactions

Use with other vaccines

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

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 *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

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

In adults ≥ 18 years of age who are immunodeficient or immunosuppressed due to disease or therapy (referred to as immunocompromised (IC)), the safety profile was consistent with that observed in adults 50 years and above.

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.

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

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.

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*.

In a clinical study including 865 adults ≥ 50 years of age, fever and shivering were reported more frequently when PPV23 vaccine was co-administered with *Shingrix* (16% and 21%, respectively) compared to when *Shingrix* was given alone (7% for both adverse reactions).

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.

Additionally, in clinical studies, 1,587 IC adults ≥ 18 years of age were vaccinated with at least 1 dose of *Shingrix*. The reported adverse reactions were consistent with those presented in the Table below.

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	lymphadenopathy
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

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: J07BK03.

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)

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 years 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 years who received at least one dose of either *Shingrix* (N=6,950) or placebo (N=6,950).

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

Two phase III, placebo-controlled, observer-blind studies evaluating *Shingrix* efficacy were conducted in IC adults ≥ 18 years with 2 doses administered 1-2 months apart:
- Zoster-002: TVC of 1,846 autologous hematopoietic stem cell transplants (aHSCT) recipients who received at least one dose of either *Shingrix* (N=922) or placebo (N=924) 50-70 days post-transplant, 21.3% (*Shingrix*) and 20.5% (placebo) of the subjects received at least one immunosuppressive (IS) treatment (for a duration of at least one day) from HSCT up to 30 days after Dose 2 (TVC). The proportion of subjects by underlying disease was: 53.1% (*Shingrix*) and 53.4% (placebo) for multiple myeloma (MM) and 46.9% (*Shingrix*) and 46.6% (placebo) for other diagnosis.
- Zoster-039: TVC of 562 subjects with hematologic malignancies who received at least one dose of either *Shingrix* (N=283) or placebo (N=279) during a cancer therapy course (37%) or after the full cancer therapy course (63%). The proportion of subjects by underlying disease was: 70.7% (*Shingrix*) and 71.3% (placebo) for MM and other disease, 14.5% (*Shingrix*) and 14.7% (placebo) for chronic lymphocytic leukaemia (CLL).

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

Incidence of HZ and PHN cases as well as vaccine efficacy were evaluated in the modified Total Vaccinated Cohort (mTVC i.e. excluding 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 compared with placebo in:
- adults ≥ 50 years (Zoster-006): 6 vs. 210 cases;
- adults ≥ 70 years (pooled analysis of Zoster-006 and Zoster-022): 25 vs. 284 cases;
- adults ≥ 18 years with aHSCT (Zoster-002): 49 vs. 135 cases;
- adults ≥ 18 years with hematologic malignancies (Zoster-039): 2 vs. 14 cases. Vaccine efficacy was calculated post-hoc.

Vaccine efficacy results against HZ are presented in Table 1.

Table 1: *Shingrix* efficacy against HZ (mTVC)

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]
Zoster-002* (aHSCT recipients[#])**							
≥ 18	870	49	30.0	851	135	94.3	**68.2** [55.5; 77.6]
18-49	213	9	21.5	212	29	76.0	**71.8** [38.7; 88.3]
≥ 50	657	40	33.0	639	106	100.9	**67.3** [52.6; 77.9]
Zoster-039 (hematologic malignancy patients[#])							
≥ 18	259	2	8.5	256	14	66.2	**87.2**** [44.2; 98.6]

CI Confidence interval
* Over a median follow-up period of 3.1 years
** Over a median follow-up period of 4.0 years
Data in subjects ≥ 70 years of age are sourced from the pre-specified pooled analyses of Zoster-006 and Zoster-022 (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

Shingrix significantly decreased the incidence of PHN compared with placebo in:
- adults ≥ 50 years (Zoster-006): 0 vs. 18 cases;
- adults ≥ 70 years (pooled analysis of Zoster-006 and Zoster-022): 4 vs. 36 cases;
- adults ≥ 18 years with aHSCT (Zoster-002): 1 vs. 9 cases

Vaccine efficacy results against PHN are presented in Table 2.

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

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]
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 Zoster-006 and Zoster-022 (mTVC) as these analyses provide the most robust estimates for vaccine efficacy in this age group.
**** Over a median follow-up period of 21 months
§ Not statistically significant.
# antiviral prophylaxis in line with the local standard of care was permitted.

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

In the fourth year after vaccination, the efficacy against HZ was 93.1% (95% CI: 81.2; 98.2) and 87.9% (95% CI: 73.3; 95.4) in subjects ≥ 50 years (Zoster-006) and subjects ≥ 70 years (pooled Zoster-006 and Zoster-022), respectively.

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

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 of HZ is the highest, the efficacy against HZ was 76.2 (95% CI: 61.1; 86.0).

Efficacy against other HZ-related complications

The evaluated HZ-related complications were: HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease including stroke, and visceral disease.

In the pooled analysis of Zoster-006 and Zoster-022, *Shingrix* significantly reduced HZ-related complications 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. No cases of visceral disease or stroke were reported during these studies.

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

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

Effect of Shingrix on HZ-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.

In Zoster-002, *Shingrix* significantly reduced the duration of severe "worst" HZ-associated pain by 38.5% (95% CI: 11.0; 57.6) in aHSCT recipients ≥ 18 years with at least one confirmed HZ episode.

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.

In adults ≥ 50 years, 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). The gE-specific immune responses (humoral and CMI) elicited by *Shingrix* are presented in Tables 3 and 4, respectively.

Table 3: Humoral immunogenicity of *Shingrix* in adults ≥ 50 years (ATP cohort for immunogenicity)

Anti-gE immune response^		
	Month 3*	Month 38**

Age group (years)	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 4: 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 for the median frequency
Q1; Q3 First and third quartiles
*** The gE-specific CD4[2+] data in the ≥ 70 YOA group were only 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.

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* in all IC populations studied are presented in Tables 5 and 6, respectively.

Table 5: Humoral immunogenicity of *Shingrix* in IC adults ≥ 18 years (ATP cohort for immunogenicity)

Anti-gE immune response^			
	Month 3		Month 13/18/25

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

ATP According-To-Protocol
^ Anti-gE immune response = anti-gE antibody levels, measured by anti-gE enzyme-linked immunosorbent assay (gE ELISA)
N Number of evaluable subjects at the specified time point (for the GMC)
CI Confidence interval
GMC Geometric Mean Concentration
Q1; Q3 First and third quartiles

Table 6: Cell-mediated immunogenicity of *Shingrix* in IC adults ≥ 18 years (ATP cohort for immunogenicity)

gE-specific CD4[2+] T cell response^					
	Month 3			Month 13/18/25	
N	Median frequency (Q1; Q3)	Median fold increase of frequency vs. pre-vaccination (Q1; Q3)	N	Median frequency (Q1; Q3)	Median fold increase of frequency vs. pre-vaccination (Q1; Q3)
Zoster-002 (aHSCT recipients)					

51	6,644.9 (1,438.3; 13,298.6)	109.0 (34.4; 2,716.4)	32	Month 13: 1,706.4 (591.4; 5,207.0)	Month 13: 43.6 (13.1; 977.8)
			30	Month 25: 2,294.4 (455.2; 3,633.2)	Month 25: 50.9 (15.3; 515.2)
Zoster-028* (solid tumour patients)					
22	778.8 (393.1; 1,098.2)	4.9 (1.7; 33.0)	18	Month 13: 332.9 (114.9; 604.6)	Month 13: 2.0 (1.3; 5.2)
Zoster-039 (hematologic malignancy patients)					
53	3,081.9 (1,766.2; 7,413.6)	45.9 (16.4; 2,221.9)	44	Month 13: 1,006.7 (416.0; 3,284.5)	Month 13: 21.4 (7.5; 351.4)
Zoster-041 (renal transplant recipients)					
32	2,149.0 (569.4; 3,695.1)	47.7 (14.7; 439.6)	33	Month 13: 1,066.3 (424.8; 1,481.5)	Month 13: 16.9 (5.9; 211.4)
Zoster-015 (HIV infected subjects)					
41	2,809.7 (1,554.5; 4,663.7)	23.4 (8.5; 604.1)	49	Month 18: 1533.0 (770.0; 2643.1)	Month 18: 12.0 (5.7; 507.0)

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 for the median frequency

Q1; Q3 First and third quartiles

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

Immunogenicity following concomitant vaccination

In four 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), PCV13 vaccine (N=912; Zoster-059) 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), 99.1% (95% CI: 97.6; 99.7) and 97.8% (95% CI: 95.8; 99.1) following co-administration of *Shingrix* with the influenza, PPV23, PCV13 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.

Version number: GDS07(SI) / Date of issue: 17 February2022

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

[GSK Logo]