PRESCRIBING INFORMATION FOR UAE
SHINGRIX
Herpes zoster vaccine (recombinant, adjuvanted)

1. NAME OF THE MEDICINAL PRODUCT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one dose (0.5 mL) contains:
Varicella Zoster Virus1 glycoprotein E antigen2,3 50 micrograms
[1]Varicella Zoster Virus = VZV
[2]adjuvanted with AS01B containing:
plant extract Quillaja saponaria Molina, fraction 21 (QS-21) 50 micrograms
3-O-desacyl-4'-monophosphoryl lipid A (MPL) from Salmonella minnesota 50 micrograms
[3]glycoprotein E (gE) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology
For the full list of excipients, see *section 6.1*.

3. PHARMACEUTICAL FORM

Powder and suspension for suspension for injection. The powder is white.
The suspension is an opalescent, colourless to pale brownish liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

The use of Shingrix should be in accordance with official recommendations

4.2 Posology and Method of Administration

Posology

The primary vaccination schedule consists of two doses of 0.5 mL each: an initial dose followed by a second dose 2 months later.
If flexibility in the vaccination schedule is necessary, the second dose can be administered between 2 and 6 months after the first dose (see section 5.1). For subjects who are or might become immunodeficient or immunosuppressed due to disease or therapy, and whom would benefit from a shorter vaccination schedule, the second dose can be given 1 to
2 months after the initial dose (see section 5.1).
The need for booster doses following the primary vaccination schedule has not been established (see section 5.1).
Shingrix can be given with the same schedule in individuals previously vaccinated with live attenuated HZ vaccine (see section 5.1).
Shingrix is not indicated for prevention of primary varicella infection (chickenpox).

Paediatric population

The safety and efficacy of Shingrix in children and adolescents have not been established.
No data are available. Method of administration
For intramuscular injection only, preferably in the deltoid muscle. For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Prior to immunisation

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.
As with other vaccines, vaccination with Shingrix should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.
As with any vaccine, a protective immune response may not be elicited in all vaccinees.
The vaccine is for prophylactic use only and is not intended for treatment of established clinical disease.

Do not administer the vaccine intravascularly or intradermally. Subcutaneous administration is not recommended.
Maladministration via the subcutaneous route may lead to an increase in transient local reactions.
Shingrix should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following intramuscular administration to these subjects.
Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.
In a post-marketing observational study in individuals aged 65 years or older, an increased risk of Guillain-Barré syndrome (estimated 3 excess cases per million doses administered) was observed during the 42 days following vaccination with Shingrix. Available information is insufficient to determine a causal relationship with Shingrix.
There are no safety, immunogenicity or efficacy data to support replacing a dose of Shingrix with a dose of another HZ vaccine.
There are limited data to support the use of Shingrix in individuals with a history of HZ (see section 5.1). Healthcare professionals therefore need to weigh the benefits and risks of HZ vaccination on an individual basis.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.
This medicine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially 'potassium-free'.

Traceability

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

4.5 Interaction with other medicinal products and other forms of interaction

Shingrix can be given concomitantly with unadjuvanted inactivated seasonal influenza vaccine, 23-valent pneumococcal polysaccharide vaccine (PPV23) or reduced antigen diphtheria-tetanus-acellular pertussis vaccine (dTpa). The vaccines should be administered at different injection sites.
In three phase III, controlled, open-label clinical studies, adults ≥ 50 years of age were randomised 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 Al3+ (N=830; Zoster-042). 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 this data is not known. The adverse reactions of fever and shivering were more frequent when PPV23 vaccine is co- administered with Shingrix. Concomitant use with other vaccines is not recommended due to lack of data.

4.6 Pregnancy , Lactation and Fertility

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effects of Shingrix on the ability to drive and use machines have been performed.
Shingrix may have a minor influence on the ability to drive and use machines in the 2-3 days following vaccination. Fatigue and malaise may occur following administration (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In adults aged 50 years and above, the most frequently reported adverse reactions were pain at the injection site (68.1% overall/dose; 3.8% severe/dose), myalgia (32.9% overall/dose; 2.9% severe/dose), fatigue (32.2% overall/dose; 3.0% severe/dose) and headache (26.3% overall/dose; 1.9% severe/dose). Most of these reactions were not long-lasting (median duration of 2 to 3 days). Reactions reported as severe lasted 1 to 2 days. In adults ≥ 18 years of age who are immunodeficient or immunosuppressed due to disease or therapy (referred to as immunocompromised (IC)), the safety profile was consistent with that observed in adults 50 years and above. There are limited data in adults aged 18-49 years at increased risk of HZ who are not IC.

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

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

Tabulated list of adverse reactions

The safety profile presented below is based on a pooled analysis of data generated in placebo- controlled clinical studies on 5,887 adults 50-69 years of age and 8,758 adults ≥ 70 years of age.

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

Adverse reactions reported during post-marketing surveillance are also tabulated 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)

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

System Organ Class[1]	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Uncommon	lymphadenopathy
Immune system disorders	Rare	hypersensitivity reactions including rash, urticaria, angioedema[2]
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

1According to MedDRA (medical dictionary for regulatory activities) terminology

2Adverse reactions from spontaneous reporting

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

By combining the VZV specific antigen (gE) with an adjuvant system (AS01B), 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 AS01B 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 AS01B is the result of interactions between MPL and QS-21 formulated in liposomes.

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:

-ZOE-50 (Zoster-006): Total Vaccinated Cohort (TVC) of 15,405 adults

≥ 50 years who received at least one dose of either Shingrix (N=7,695) or placebo (N=7,710).

-ZOE-70 (Zoster-022): TVC of 13,900 adults ≥ 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 diseases, 14.5% (Shingrix) and 14.0% (placebo) for non-Hodgkin B-cell lymphoma (NHBCL) and 14.8% (Shingrix) and 14.7% (placebo) for chronic lymphocytic leukaemia (CLL).

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

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

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

-adults ≥ 50 years (ZOE-50): 6 vs. 210 cases;

-adults ≥ 70 years (pooled analysis of ZOE-50 and ZOE-70): 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	
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** [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

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

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

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

Vaccine efficacy results against PHN are presented in Table 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	
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. A further reduction of PHN incidence in subjects with confirmed HZ could not be demonstrated due to the limited number of HZ cases in the vaccine group.
In the fourth year after vaccination, the efficacy against HZ was 93.1% (95% CI: 81.2; 98.2) and 87.9% (95% CI: 73.3; 95.4) in adults ≥ 50 years (ZOE-50)
and adults ≥ 70 years (pooled ZOE-50 and ZOE-70), respectively.
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 for HZ is the highest, the efficacy against HZ was 76.2% (95% CI: 61.1; 86.0).

Efficacy against HZ-related complications other than PHN

The evaluated HZ-related complications (other than PHN) were: HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease including stroke, and visceral disease. In the pooled analysis of ZOE-50 and ZOE-70, Shingrix significantly reduced these HZ-related complications by 93.7% (95% CI: 59.5; 99.9) and 91.6% (95% CI: 43.3; 99.8) in adults
≥ 50 years (1 vs. 16 cases) and adults ≥ 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-related pain

Overall in ZOE-50 and ZOE-70 there was a general trend towards less severe HZ-related pain in subjects vaccinated with Shingrix compared to placebo. As a consequence of the high vaccine efficacy against HZ, a low number of breakthrough cases were accrued, and it was therefore not possible to draw firm conclusions on these study objectives.
In subjects ≥ 70 years with at least one confirmed HZ episode (ZOE-50 and ZOE-70 pooled), Shingrix significantly reduced the use and the duration of HZ-related pain medication by 39.0% (95% CI: 11.9; 63.3) and 50.6% (95% CI: 8.8; 73.2), respectively. The median duration of pain medication use was
32.0 and 44.0 days in the Shingrix and placebo group, respectively.
In subjects with at least one confirmed HZ episode, Shingrix significantly reduced the maximum average pain score versus placebo over the entire HZ episode (mean = 3.9 vs. 5.5, P-value = 0.049 and mean = 4.5 vs. 5.6,
P-value = 0.043, in subjects ≥ 50 years (ZOE-50) and ≥ 70 years (ZOE-50 and ZOE-70 pooled), respectively). In addition, in subjects ≥ 70 years (ZOE-50 and ZOE-70 pooled), Shingrix significantly reduced the maximum worst pain score versus placebo over the entire HZ episode (mean = 5.7 vs. 7.0,
P-value = 0.032).
The burden-of-illness (BOI) score incorporates the incidence of HZ with the severity and duration of acute and chronic HZ-related pain over a 6 month period following rash onset.
The efficacy in reducing BOI was 98.4% (95% CI: 92.2; 100) in subjects
≥ 50 years (ZOE-50) and 92.1% (95% CI: 90.4; 93.8) in subjects ≥ 70 years (ZOE-50 and ZOE-70 pooled).
In Zoster-002, Shingrix significantly reduced the duration of severe 'worst' HZ-associated pain by 38.5% (95% CI: 11.0; 57.6) in aHSCT recipients
≥ 18 years with at least one confirmed HZ episode. Shingrix significantly reduced the maximum average pain score versus placebo over the entire HZ episode (mean = 4.7 vs. 5.7, P-value = 0.018) and the maximum worst pain score versus placebo over the entire HZ episode (mean = 5.8 vs. 7.1,
P-value = 0.011).

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

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

Immunogenicity of Shingrix

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

In adults ≥ 50 years, the immune responses to Shingrix, given as 2 doses 2 months apart, were evaluated in a subset of subjects from the phase III efficacy studies ZOE-50 [humoral immunity and cell-mediated immunity (CMI)] and ZOE-70 (humoral immunity). The gE-specific immune responses (humoral and CMI) elicited by Shingrix are presented in Tables 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**	**GMC (mIU/mL) (95% CI)**	**Median fold increase of concentrations vs. pre- vaccination (Q1; Q3)**	**N**	**GMC (mIU/mL) (95% CI)**	**Median fold increase of concentrations vs. pre- vaccination (Q1; Q3)**
ZOE-50						
≥ 50	1,070	52,376.6 (50,264.1; 54,577.9)	**41.9** (20.8; 86.9)	967	11,919.6 (11,345.6; 12,522.7)	**9.3** (4.9; 19.5)
Pooled ZOE-50 and ZOE-70						
≥ 7074	2	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) 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^						
	Month 3*			**Month 38****		
Age group (years)			**Median fold increase of**			**Median fold increase of**

	N	Median frequency (Q1; Q3)	frequency vs. pre- vaccination (Q1; Q3)	N	Median frequency (Q1; Q3)	frequency vs. pre- vaccination (Q1; Q3)
ZOE-50						
≥ 50164		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 years of age group were only generated in ZOE-50 because CD4+ T cell activity was not assessed in ZOE-70

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 approximately 6 years 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, given as 2 doses 1-2 months apart, were evaluated in:

-one phase I/II study: Zoster-015 (HIV infected subjects, the majority (76.42%) being stable on antiretroviral therapy (for at least one year) with a CD4 T-cell count ≥200 /mm3);

-one phase II/III study: Zoster-028 (patients with solid tumours undergoing chemotherapy);

-three phase III studies: Zoster-002 (aHSCT recipients vaccinated post-transplant), Zoster-039 (patients with hematologic malignancies vaccinated during a cancer therapy course or after the full cancer therapy course) and Zoster-041 (renal transplant recipients on chronic immunosuppressive treatment at the time of vaccination).

The gE-specific immune responses (humoral and CMI) elicited by Shingrix in all IC populations studied are presented in Tables 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	Median fold increase of concentrations vs	N	GMC	Median fold increase of concentrations vs

	(mIU/mL) (95% CI)	pre-vaccination (Q1; Q3)		(mIU/mL) (95% CI)	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

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.

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**	
		Median fold increase of			**Median fold increase of frequency vs.**

N	Median frequency (Q1; Q3)	frequency vs. pre- vaccination (Q1; Q3)	N	Median frequency (Q1; Q3)	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 in subjects receiving 2 doses of Shingrix 6 months apart

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

In a phase III, open-label clinical study (Zoster-026) where 238 adults ≥ 50 years of age were equally randomised to receive 2 doses of Shingrix 2 or 6 months apart, the humoral immune response following the 0, 6-month schedule was demonstrated to be non-inferior to the response with the 0, 2- month schedule. The anti-gE GMC at 1 month after the last vaccine dose was 38,153.7 mIU/mL (95% CI: 34,205.8; 42,557.3) and 44,376.3 mIU/mL (95%CI: 39,697.0; 49,607.2) following the 0, 6-month schedule and the 0, 2-month schedule, respectively.

Subjects with a history of HZ prior to vaccination

Subjects with a history of HZ were excluded from ZOE-50 and ZOE-70. In a phase III, uncontrolled, open-label clinical study (Zoster-033), 96 adults ≥ 50 years of age with a physician-documented history of HZ received 2 doses of Shingrix 2 months apart. Laboratory confirmation of HZ cases was not part of the study procedures. The anti-gE GMC at 1 month after the last vaccine dose was 47,758.7 mIU/mL (95% CI: 42,258.8; 53,974.4). There were 9 reports of suspected HZ in 6 subjects over a one-year follow up period. This is a

higher recurrence rate than generally reported in observational studies in unvaccinated individuals with a history of HZ. (See section 4.4)

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

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

Paediatric population

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

After reconstitution:

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

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

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

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

6. 6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder (gE antigen):

Sucrose
Polysorbate 80 (E 433)
Sodium dihydrogen phosphate dihydrate (E 339)
Dipotassium phosphate (E 340)

Suspension (AS01B Adjuvant System):

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

For adjuvant see also section 2.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After reconstitution:

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

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

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

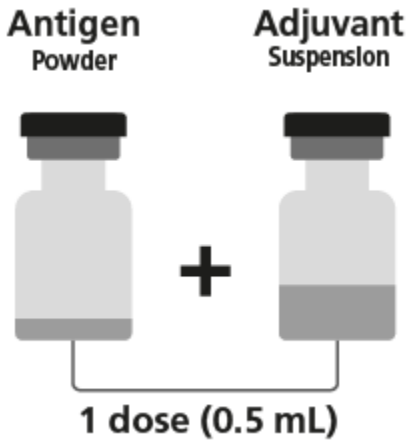
6.5 Nature and contents of container

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

Shingrix is available in a pack size of 1 vial of powder 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 marketed

6.6 Special precautions for disposal and other handling

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



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

How to prepare Shingrix:

Shingrix must be reconstituted prior to administration.
1. Withdraw the entire contents of the vial containing the suspension into 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.

7. 7.MARKETING AUTHORISATION HOLDER & MANUFACTURERS

Marketing Authorization Holder:

GlaxoSmithKline Biologicals S.A.
Rue de l'Institut 89, B-1330 Rixensart Belgium
Bulk Manufacturing for Antigen and Adjuvant: GlaxoSmithKline Biologicals S.A.
Parc de la Noire Epine Avenue Fleming 20, 1300 Wavre, Belgium
Primary Packaging for Antigen:
GlaxoSmithKline Biologicals
Rue des Aulnois 637, 59230 Saint-Amand-Les-Eaux, France
Primary Packaging for Adjuvant:
GlaxoSmithKline Biologicals S.A.
Parc de la Noire Epine Avenue Fleming 20, 1300 Wavre, Belgium
Secondary Packaging for Antigen and Adjuvant: GlaxoSmithKline Vaccines S.r.l.
Bellaria-Rosia, 53018 Sovicille, Italy
Batch releaser:
GlaxoSmithKline Biologicals S.A.
Rue de l'Institut 89, B-1330 Rixensart Belgium

8. 8.DATE OF REVISION

11/03/2021

Detailed information on this medicinal product can be requested via: gcc.medinfo@gsk.com.
To report Adverse Event/s associated with the use of GSK product/s, please contact us via gulf.safety@gsk.com.
All Quality complaints should be reported to the LOC Quality department mail box Gulf-KSA.Product-Complaints@gsk.com

Prescribing information for UAE Prepared September 2022 from the summary of product characteristics version with Date of first authorisation: 18/05/2022