ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Shingrix powder and suspension for suspension for injection
Herpes zoster vaccine (recombinant, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one dose (0.5 ml) contains:
Varicella Zoster Virus[1] glycoprotein E antigen[2,3] 50 micrograms

[1] Varicella Zoster Virus = VZV
[2] adjuvanted with $AS01_B$ 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 Ovarian (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 (see section 5.1).

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).

The need for booster doses following the primary vaccination schedule has not been established (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

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.

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.

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 and in frail individuals including those with multiple comorbidities (see section 5.1). Healthcare professionals therefore need to weigh the benefits and risks of HZ vaccination on an individual basis.

Systemic immunosuppressive medications and immunodeficiency

Safety and immunogenicity data on a limited number of immunocompromised subjects with human immunodeficiency virus (HIV) or haematopoietic stem cell transplant (HCT) are available (see section 5.1). The use of Shingrix in subjects with other confirmed or suspected immunosuppressive or immunodeficient conditions is under investigation.
As with other vaccines, an adequate immune response may not be elicited in these individuals. The administration of Shingrix to immunocompromised subjects should be based on careful consideration of potential benefits and risks.

4.5 Interaction with other medicinal products and other forms of interaction

Shingrix can be given concomitantly with unadjuvanted inactivated seasonal influenza vaccine. The vaccines should be administered at different injection sites.

In a phase III, controlled, open-label clinical study (Zoster-004), 828 adults ≥ 50 years of age were randomised to receive 2 doses of Shingrix 2 months apart administered either concomitantly at the first dose (N=413) or non-concomitantly (N=415) with an unadjuvanted inactivated seasonal influenza vaccine. The antibody responses to both vaccines were similar, whether administered concomitantly or non-concomitantly.

Concomitant use with other vaccines is not recommended due to lack of data.

4.6 Fertility, pregnancy and lactation

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

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.

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.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 ($AS01_B$), 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.

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:
- ZOE-50 (Zoster-006): 15,405 adults ≥ 50 years were randomised to receive two doses of either Shingrix (N=7,695) or placebo (N=7,710) administered 2 months apart,
- ZOE-70 (Zoster-022): 13,900 adults ≥ 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 against HZ and PHN observed 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, 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 ZOE-50) and in subjects ≥ 70 years (25 vs. 284 cases in the pooled analysis of ZOE-50 and ZOE-70).

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	
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]

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.

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 (0 vs. 18 cases in ZOE-50) and in adults ≥ 70 years (4 vs. 36 cases in the pooled analysis of ZOE-50 and ZOE-70).

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	
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]

* 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.
§ 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 adults ≥ 50 years and adults ≥ 70 years, respectively.

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

Efficacy against HZ-related complications other than PHN

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

Effect of Shingrix on HZ-related pain

Overall 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).

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 ZOE-50 [humoral immunity and cell-mediated immunity (CMI)] and ZOE-70 (humoral immunity). Shingrix elicited higher gE-specific immune responses (humoral and CMI) at 1 month post-dose 2 when compared to pre-vaccination levels.

The humoral immunogenicity and CMI results 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^						
Age group (years)	Month 3*			Month 38**		
	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						
≥ 70	742	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^						
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)
ZOE-50						
≥ 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 years of age group were 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.

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)

Immunocompromised subjects

Two phase I/II clinical studies, Zoster-001 and Zoster-015, were conducted in subjects with autologous hematopoietic stem cell transplant or HIV infection. A total of 135 adults, of whom 73 were ≥50 years of age, received at least one dose of Shingrix, which was shown to be immunogenic and well-tolerated.

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).

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. PHARMACEUTICAL PARTICULARS

6.1 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

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

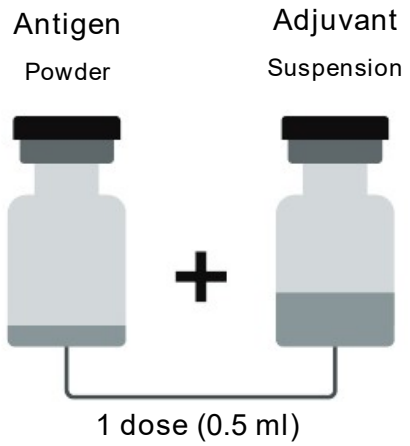
- Powder for 1 dose in a vial (type I glass) with a stopper (butyl rubber)
- Suspension for 1 dose in a vial (type I glass) with a stopper (butyl rubber).

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. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals S.A.
Rue de l'Institut 89
B-1330 Rixensart
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1272/001
EU/1/18/1272/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SYPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS FOR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

GlaxoSmithKline Biologicals SA
Parc de la Noire Epine
20, Avenue Fleming
1300 Wavre
BELGIUM

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Biologicals SA
Rue de l'Institut, 89
1330 Rixensart
BELGIUM

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- Official batch release

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or

as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1 VIAL AND 1 VIAL
10 VIALS AND 10 VIALS

1. NAME OF THE MEDICINAL PRODUCT

Shingrix powder and suspension for suspension for injection
Herpes zoster vaccine (recombinant, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.5 ml) contains 50 micrograms of recombinant Varicella Zoster Virus glycoprotein E adjuvanted with $AS01_B$

3. LIST OF EXCIPIENTS

Excipients:
sucrose
polysorbate 80
sodium dihydrogen phosphate dihydrate
dipotassium phosphate
dioleoyl phosphatidylcholine
cholesterol
sodium chloride
disodium phosphate anhydrous
potassium dihydrogen phosphate
water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and suspension for suspension for injection
1 vial: powder (antigen)
1 vial: suspension (adjuvant)

10 vials: powder (antigen)
10 vials: suspension (adjuvant)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

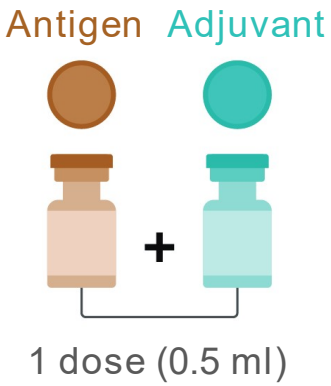
Read the package leaflet before use.
Intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Powder and suspension to be reconstituted before administration



8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1272/001 – 1 vial and 1 vial
EU/1/18/1272/002 – 10 vials and 10 vials

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Antigen for Shingrix
I.M.

2. METHOD OF ADMINISTRATION

Mix with adjuvant

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH SUSPENSION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Adjuvant for Shingrix

2. METHOD OF ADMINISTRATION

Mix with antigen

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Shingrix powder and suspension for suspension for injection
Herpes zoster vaccine (recombinant, adjuvanted)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Shingrix is and what it is used for

What Shingrix is used for
Shingrix is a vaccine that helps to protect adults against shingles (herpes zoster) and post-herpetic neuralgia (PHN), the long-lasting nerve pain that follows shingles.

Shingrix is given to adults 50 years and above.

Shingrix cannot be used to prevent chickenpox (varicella).

What shingles is
- Shingles is a rash with blisters that is often painful. It usually occurs in one part of the body and can last for several weeks.
- Shingles is caused by the same virus that causes chickenpox.
- After you have had chickenpox, the virus that caused it stays in your body in nerve cells.
- Sometimes, after many years, if your immune system (the body's natural defences) becomes weaker (due to age, an illness or a medicine you are taking), the virus can cause shingles.

Complications related to shingles
Shingles may lead to complications.
The most common complication of shingles is:
- long-lasting nerve pain – called post-herpetic neuralgia or PHN. After the shingles blisters heal, you may get pain which can last for months or years and may be severe.

Other complications of shingles are:
- scars where the blisters have been.
- skin infections, weakness, muscle paralysis and loss of hearing or vision – these are less common.

How Shingrix works
Shingrix reminds your body about the virus that causes shingles. This helps your immune system (the body's natural defences) stay prepared to fight the virus and protect you against shingles and its complications.

2. What you need to know before you receive Shingrix

You should not receive Shingrix if:
- you are allergic (hypersensitive) to the active substances or any of the other ingredients of this vaccine (listed in section 6). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

You should not receive Shingrix if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist.

Warnings and precautions
Talk to your doctor or pharmacist before you receive Shingrix if:
- you have a severe infection with a high temperature (fever). In these cases, the vaccination may have to be postponed until you have recovered. A minor infection such as a cold should not be a problem, but talk to your doctor first;
- you have a bleeding problem or bruise easily.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before you receive Shingrix.

Fainting can occur before or after any needle injection. Therefore tell the doctor or nurse if you fainted with a previous injection.

Shingrix cannot be used as a treatment if you already have shingles or shingles-related complications.

As with all vaccines, Shingrix may not fully protect all people who are vaccinated.

Other medicines and Shingrix
Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription, or have recently received any other vaccine.

Shingrix can be given at the same time as a flu vaccine known as 'unadjuvanted inactivated seasonal influenza vaccine'. A different injection site will be used for each vaccine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this vaccine.

Driving and using machines
It is not known if Shingrix affects your ability to drive or use machines. However, do not drive or use machines if you are feeling unwell.

Shingrix contains sodium and potassium
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'.

3. How Shingrix is given

- Shingrix is given as an injection into a muscle (usually in the upper arm).

- You will receive 2 injections with an interval of 2 months. If flexibility in the vaccination schedule is necessary, the second dose can be administered between 2 and 6 months after the first dose. The first injection can be given from the age of 50 years onwards.
- You will be informed when you should come back for the second dose of Shingrix.

Make sure you finish the complete vaccination course. This will maximise the protection offered by Shingrix.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

Very common (these may occur with more than 1 in 10 doses of the vaccine):
- headache
- stomach and digestive complaints (including nausea, vomiting, diarrhoea and/or stomach pain)
- muscle pain (myalgia)
- pain, redness and swelling where the injection is given
- feeling tired, chills, fever

Common (these may occur with up to 1 in 10 doses of the vaccine):
- itching where the injection is given (pruritus)
- generally feeling unwell

Uncommon (these may occur with up to 1 in 100 doses of vaccine)
- swollen glands in the neck, armpit or groin
- joint pain

Most of these side effects are mild to moderate in intensity and are not long-lasting.

Adults aged 50-69 years may experience more side effects compared to adults aged ≥ 70 years.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Shingrix

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C – 8°C).
- Do not freeze.
- Store in the original package in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Shingrix contains

- The active substances are:

  After reconstitution, one dose (0.5 ml) contains:
  Varicella Zoster Virus[1] glycoprotein E antigen[2] 50 micrograms

  [1] Varicella Zoster Virus = VZV
  [2] adjuvanted with $AS01_B$ 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

  The glycoprotein E is a protein present in the Varicella Zoster Virus. This protein is not infectious.

  The adjuvant ($AS01_B$) is used to improve the body's response to the vaccine.

- The other ingredients are:

  - Powder: Sucrose, polysorbate 80, sodium dihydrogen phosphate dihydrate, dipotassium phosphate.
  - Suspension: Dioleoyl phosphatidylcholine, cholesterol, sodium chloride, disodium phosphate anhydrous, potassium dihydrogen phosphate and water for injections.

What Shingrix looks like and contents of the pack

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

One pack of Shingrix consists of:
- Powder for 1 dose in a vial
- Suspension for 1 dose in a vial

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

Marketing Authorisation Holder and Manufacturer

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Belgique/België/Belgien
GlaxoSmithKline Pharmaceuticals s.a./n.v.
Tél/Tel: + 32 10 85 52 00

Lietuva
GlaxoSmithKline Lietuva UAB
Tel: +370 5 264 90 00
info.lt@gsk.com

България
ГлаксоСмитКлайн ЕООД
Тел. + 359 2 953 10 34

Luxembourg/Luxemburg
GlaxoSmithKline Pharmaceuticals s.a./n.v.
Tél/Tel: + 32 10 85 52 00

Česká republika
GlaxoSmithKline s.r.o.
Tel: + 420 2 22 00 11 11
cz.info@gsk.com

Danmark
GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
dk-info@gsk.com

Deutschland
GlaxoSmithKline GmbH & Co. KG
Tel: + 49 (0)89 360448701
produkt.info@gsk.com

Eesti
GlaxoSmithKline Eesti OÜ
Tel: +372 667 6900
estonia@gsk.com

Ελλάδα
GlaxoSmithKline A.E.B.E
Τηλ: + 30 210 68 82 100

España
GlaxoSmithKline, S.A.
Tel: + 34 902 202 700
es-ci@gsk.com

France
Laboratoire GlaxoSmithKline
Tél: + 33 (0) 1 39 17 84 44
diam@gsk.com

Hrvatska
GlaxoSmithKline d.o.o.
Tel.: + 385 (0)1 6051999

Ireland
GlaxoSmithKline (Ireland) Ltd
Tel: + 353 (0)1 495 5000

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
GlaxoSmithKline S.p.A.
Tel: + 39 (0)45 9218 111

Magyarország
GlaxoSmithKline Kft.
Tel.: + 36-1-2255300

Malta
GlaxoSmithKline (Malta) Ltd
Tel: + 356 21 238131

Nederland
GlaxoSmithKline BV
Tel: + 31 (0)30 69 38 100
nlinfo@gsk.com

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00

Österreich
GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

Polska
GSK Services Sp. z o.o.
Tel.: + 48 (22) 576 9000

Portugal
GlaxoSmithKline - Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România
GlaxoSmithKline (GSK) SRL
Tel: +40 (0)21 3028 208

Slovenija
GlaxoSmithKline d.o.o.
Tel: + 386 (0) 1 280 25 00
medical.x.si@gsk.com

Slovenská republika
GlaxoSmithKline Slovakia s.r.o.
Tel.: + 421 (0)2 48 26 11 11
recepcia.sk@gsk.com

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 10 30 30 30
Finland.tuoteinfo@gsk.com

Κύπρος
GlaxoSmithKline (Cyprus) Ltd
Τηλ: + 357 22 39 70 00
gskcyprus@gsk.com

Latvija
GlaxoSmithKline Latvia SIA
Tel: + 371 67312687
lv-epasts@gsk.com

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

United Kingdom
GlaxoSmithKline UK
Tel: +44 (0)800 221 441
customercontactuk@gsk.com

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website

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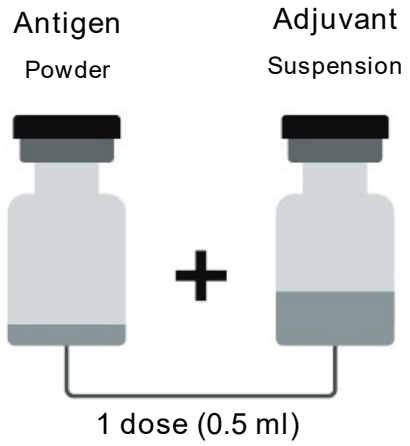
The following information is intended for healthcare professionals only:

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.

<u>How to prepare Shingrix:</u>

Shingrix must be reconstituted prior to administration.

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