Module 1.8.2

European Union Risk Management Plan (EU-RMP) for *Shingrix*

RMP version to be assessed as part of this application	
RMP Version number	12.3
Data lock point for this RMP	07 March 2025
Date of final sign off	06 October 2025

Rationale for submitting an updated RMP:

This RMP update consolidates version 12.2 with version 10.0 to include the new Shingrix formulation, fully liquid suspension for injection.

Summary of significant changes in this RMP:

PART	**MODULE**	**Changes made in the present EU-RMP**
I	Part I: Product Overview	Part I updated to reflect new Shingrix formulation, fully liquid suspension for injection

Other RMP versions under evaluation

RMP Version number	**Submitted on**	**Procedure number**
None		

Details of the currently approved RMP

Version number	Approved with procedure	Date of approval (opinion date)
12.2	EMA/VR/0000263592	02 October 2025

QPPV Name	Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety & Pharmacovigilance and EU QPPV
QPPV Signature	Electronic signature on file

ABBREVIATIONS

AE	Adverse Event
AR	Attributable risk
AS	Adjuvant System
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CMI	Cell-Mediated Immunity
DLP	Data Lock Point
EEA	European Economic Area
EMA	European Medicines Agency
GBS	Guillain-Barré syndrome
gE	glycoprotein E
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
HSCT	Hematopoietic Stem Cell Transplantation
HZ	Herpes Zoster
HZO	Herpes Zoster Ophthalmicus
IC	Immunocompromised
IM	Intramuscular
µg	Micrograms
MPL	3-O-desacyl-4'-monophosphoryl lipid A
O/E	Observed/Expected
PASS	Post-Authorization Safety Study
pIMDs	Potential Immune-Mediated Disorders
PT	Preferred Term
PHN	Post Herpetic Neuralgia
PPV	Positive Predictive Value
PV	Pharmacovigilance
PY	Person-Years
QS-21	*Quillaja saponaria* Molina fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid arthritis
RR	Relative Risk
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
su	Subunit
TTO	Time to Onset
TSS	Targeted Safety Study
US	United States
VE	Vaccine Efficacy
VZV gE	Varicella Zoster Virus (VZV) glycoprotein E
YOA	Years Of Age

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
Shingrix

Trademarks not owned by the GlaxoSmithKline group of companies
BCHT
Biken
SkyZoster
Varivax
Zostavax

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LIST OF ANNEXES

PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) (INN or common name)	Herpes zoster vaccine (recombinant, adjuvanted)
Pharmacotherapeutic group(s) (ATC Code)	J07BK03
Marketing Authorization Holder/ Applicant	GlaxoSmithKline Biologicals SA
Medicinal products to which this RMP refers	Herpes zoster vaccine (recombinant, adjuvanted)
Invented name(s) in the European Economic Area (EEA)	Shingrix
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: *Shingrix* is a non-live adjuvanted recombinant Varicella Zoster Virus (VZV) glycoprotein E (gE) subunit (su) vaccine. 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. *Shingrix* is to be administered intramuscularly following a 2-dose schedule (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). 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. Shingrix contains the recombinant VZV gE antigen as active substance and the $AS01_B$ Adjuvant System. The lyophilized fraction containing the VZV gE antigen (50 micrograms [µg]) and formulation excipients is presented as a monodose in 3 mL glass vial. The liquid fraction consisting of $AS01_B$ Adjuvant System is presented as a 0.5 mL monodose in 3 mL glass vial. The liquid $AS01_B$ Adjuvant System is used to reconstitute the lyophilized antigen, immediately prior to administration.

	Summary of mode of action: VZV gE is the most abundant VZV glycoprotein present in the envelope of virions, and also highly expressed on the surface of virus-infected cells. gE plays a central role during initiation of viral infection and disease progression. It is a major target for neutralizing antibodies and cell mediated immune (CMI) response. Data from completed clinical trials demonstrated the ability of the vaccine to induce strong and sustained cellular and humoral immune responses in individuals who are at increased risk of developing HZ.
	Important information about its composition: The gE antigen is a purified recombinant protein produced in Chinese Hamster Ovary (CHO) cells. The $AS01_B$ Adjuvant System contains 50 µg of each of the immuno-enhancers *Quillaja saponaria* Molina, fraction 21 (QS-21) and 3-O-desacyl-4'- monophosphoryl lipid A (MPL) combined with liposomes.
Reference to the Product Information	Please refer to the approved product information (Section 1.3.1 of the eCTD).
Indication(s) in the EEA	Current: 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.
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current: 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. 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. The need for booster doses following the primary vaccination schedule has not been established.

	Shingrix can be given with the same schedule in individuals previously vaccinated with live attenuated HZ vaccine.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current: Powder and suspension for suspension for injection. The powder is white. The suspension is an opalescent, colourless to pale brownish liquid. 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 Ovary (CHO) cells by recombinant DNA technology
	Proposed (if applicable): Suspension for injection. One dose (0.5ml) contains 50 micrograms of gE antigen adjuvanted with $AS01_B$. The suspension is an opalescent, colourless to pale brownish liquid.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 INDICATION

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

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

Incidence

HZ disease occurs worldwide. About 1 in 3 persons will develop HZ during their lifetime [Balfour, 1988; Thomas, 2004]. Evidence from studies have shown that the epidemiology of HZ is similar across Europe, North America and Japan. In the general population and considering all ages, the overall incidence rate of HZ is approximately 3 to 6 per 1000 person-years (PY) [Kawai 2014]. The incidence of HZ increases with age from about 1-4 per 1,000 PY in adults aged 40– 50 years, 7-8 per 1,000 PY in 60-70 years old, up to 10 per 1,000 PY after 80 years of age (YOA) with approximately 1.7 million new cases of HZ expected in Europe per year [Pinchinat 2013].

Studies have shown that adults >18 YOA who are immunocompromised or immunosuppressed from medical conditions and/or treatments have a higher risk for HZ when compared to older adults >50 years in the general population [Marra, 2020; Marra, 2016; Liu, 2015; Staikov, 2014]. The HZ disease burden in these individuals is expected to increase over time in the absence of immunization and due to longer life expectancy resulting from improvements in medical managements and new indications for immunosuppressive treatments.

Prevalence

The prevalence of HZ is not well known and is based mostly on self-reported data from surveys or medical records. Using nationally representative survey data, the lifetime prevalence of HZ among the study sample in England was 11.5% (12.6% among women, 10.3% among men), which increased with age [Cadogan, 2022]. Among patients who are immunocompromised, the prevalence of HZ is also not well known but varies by type and degree of immunosuppression, underlying disease and the age of the patient.

SI.1.1 Demographics of the population in the authorized indication and risk factors for the disease

HZ risk factors

The main risk factors for developing HZ include:

- Increasing age: steep rise in incidence with age assumed to be due to waning cell-mediated immunity (immunosenescence).
- Immunodeficiency/Immunosuppression due to disease and/or therapies.
- Other conditions which impair the immune system and for which the immune altering mechanism is less well defined (for example, chronic diseases [asthma, Type-2 diabetes, etc.], as well as stress, depression, family history, or a history of a previous episode of HZ).

Age

The incidence of HZ increases with age. The incidence of HZ in different age groups is summarized in Table 2.

Table 2 HZ incidence rate in different age groups

Age	HZ incidence rate	References
18-34 YOA	1.0 to 2.8 per 1000 PY	Leung, 2011; Harpaz, 2019
35-44 YOA	1.4 to 4.8 per 1000 PY	Harpaz, 2019
45-55 YOA	2.3 to 6.6 per 1000 PY	Harpaz, 2019
18-49 YOA	3.4 per 1000 PY	Chen, 2014a
50-59 YOA	6.4 per 1000 PY	
60-64 YOA	7.7 per 1000 PY	
≥65 YOA	8.4 per 1000 PY	
30-49 YOA	2.2 to 4.8 per 1000 PY	Harpaz, 2019
<50 YOA	1.0 to 4.8 per 1000 PY	Insinga, 2005; Leung, 2011; Harpaz, 2019

In addition, the incidence of HZ complications also increases with age. PHN is rare in HZ cases <50 YOA but increases to 20-30% in HZ cases ≥70 YOA [Oxman, 2005; Scott, 2006].

Immunodeficiency/Immunosuppression

The exact mechanism of VZV reactivation is unknown, but it is thought to involve a decline in cell mediated immunity (CMI). Immunocompromised (IC) subjects have impaired CMI, due to underlying disease or immunosuppressive therapies, putting them at risk for VZV reactivation and consequently HZ. Immunodeficiency/ immunosuppression is also associated with increased risk of severe disease such as disseminated HZ, PHN, and related complications, requiring much more healthcare resource utilization and increased healthcare cost. The incidence of HZ in different immunodeficient/immunosuppressed conditions is summarized in Table 3.

Table 3 HZ incidence rate in immunodeficient/immunosuppressed conditions

Immunodeficient / Immunosuppressed condition	HZ incidence rate	References
Bone marrow or stem cell transplantation (allogeneic, syngeneic and autologous)	41.7-51.3 per 1000 PY	Chen, 2014a; McKay, 2020, Sahoo, 2017; Yanni, 2018
Solid organ transplant	12.1-31.6 per 1000 PY	Arness, 2008; Chen, 2014a; Koo, 2014; McKay, 2020; Pergam, 2011; Yanni, 2018
Cancer (during chemotherapy)	13.8-23.0 per 1000 PY	Chen, 2014a; Habel, 2013; Mao, 2018; Qian, 2019
Human Immunodeficiency Virus (HIV) infected individuals	9.3-17.4 per 1000 PY	Blank, 2012; Chen, 2014a
Medication to treat moderate to severe rheumatoid arthritis or inflammatory bowel disease	5.6-14.3 per 1000 PY	Chen, 2014a; Khan, 2018; McDonald, 2009; Strangefeld, 2009; Winthrop, 2013

Other potential risk factors

Other potential risk factors for HZ include gender, ethnicity/race, genetic predisposition, physical trauma, some psychological conditions, and chronic diseases (Table 4).

Table 4 Potential HZ risk factors

Potential HZ risk factors	Higher HZ incidence	References
Gender	Women	Thomas, 2004; Opstelten, 2006; Pinchinat, 2013; Kawai, 2017
Ethnicity/race	Caucasians and non-Hispanic Whites	Schmader, 1995; Chaves, 2007; Kawai, 2017; Marra, 2020
Trauma	Recent physical trauma	Zhang, 2013; Marra, 2020
Genetic predisposition	Family history of HZ and prior HZ history	Lasserre, 2012; Kawai, 2017; Suo, 2017
Psychological condition	Stress and depression	Lasserre, 2012; Liao, 2015; Marin, 2016; Choi, 2019; Marra, 2020
Chronic Disease	Asthma, chronic obstructive pulmonary disease, kidney disease, and diabetes mellitus	Kwon, 2016; Kawai, 2017; Hamad, 2021; Li, 2021

Impact of external and internal boosting on VZV immune status and impact of varicella universal mass vaccination on HZ epidemiology

External boosting (exposure to exogenous VZV via contact with individuals with active VZV infection) and internal boosting (reactivation of endogenous VZV) may play a role in maintaining VZV immunity, however these mechanisms are not well understood [Reynolds, 2008].

Exposure to wild-type VZV in persons with latent wild-type VZV infection is thought to boost specific immunity, which could contribute to controlling reactivation of VZV and to reduce the development of shingles [Thomas, 2002; Donahue, 2010]. Even if enough varicella exposures could reduce the risk of HZ in highly exposed individuals, it is still unclear whether varicella exposure reduces the risk for HZ among the general population of older adults and it is also unclear how long this effect would last [Harpaz, 2008]. Models have suggested that mass vaccination against varicella would lead to fewer opportunities for varicella exposure among persons with previous wild-type varicella infection and thus increase the risk for HZ [Brisson, 2002; Reynolds, 2008]. However, these models rely on several assumptions and they cannot substitute for clinical and epidemiological data.

Moreover, epidemiological studies [Jumaan, 2005; Yih, 2005; Hales, 2013] and active surveillance data [Spells, 2008; Civen, 2009] have not documented any consistent trends in HZ incidence in the US since implementation of universal childhood varicella vaccination program in 1995 [Marin, 2007]. Similar findings are observed in Canada and in the United Kingdom, where reported increases in HZ incidence were not associated with a varicella vaccination program [Brisson, 2001; Russell, 2007]. In Germany, so far, the sentinel network for surveillance of varicella and HZ did not identify significant changes in HZ incidence in relation to varicella vaccination [Siedler, 2010].

SI.1.2 The main existing treatment options

Therapeutic measures for the management of HZ and acute HZ pain

In immunocompetent adults, antiviral therapy has been shown to decrease the duration of the HZ rash and the severity of pain associated with the rash, in particular in patients who received treatment within 72 hours after the onset of rash. Systemic antiviral therapy (for example: acyclovir, famciclovir, valacyclovir, or brivudine) is recommended as first line treatment for all immunocompetent subjects with HZ who fulfill any of the following criteria: (1) Age $\geq$50 years; (2) Moderate or severe pain; (3) Moderate or severe rash; or (4) Non-truncal involvement [Dworkin, 2007a].

In IC individuals, antiviral therapy is recommended even if the onset of rash is after 72 hours. Parenteral antivirals are the first line of therapy although oral antivirals can be used in individuals with mild disease [Stevens, 2014]. VZV immunoglobulins and antiviral agents might be given prophylactically to prevent HZ [Cohen, 2008].

A variety of approaches have also been used with varying degrees of success for control of acute HZ pain, including acetaminophen, non-steroidal anti-inflammatory agents, tricyclic antidepressants, opioids, anticonvulsants, capsaicin, and topical anesthetics [Dworkin, 2007b].

Therapeutic measures for the management of chronic pain

A Cochrane review, which considered all randomized controlled trials of antiviral treatment given within 72 hours after the onset of HZ for preventing PHN, showed that oral acyclovir does not reduce the incidence of PHN, while there is insufficient evidence to determine the effect of other antiviral treatments [Chen, 2014b]. Furthermore, the addition of systemic glucocorticoids to antiviral drugs during the acute phase of HZ does not reduce the incidence of PHN [Wood 1994; Whitley 2010].

Treatment of PHN is aimed to control symptoms, as no disease-modifying therapy is currently available [van Wijck, 2006]. Treatment may involve topical therapy such as lidocaine or capsaicin as first-line treatment for mild pain and systemic therapy, generally with anti-epileptic drugs gabapentin and pregabalin, or tricyclic antidepressants [Johnson, 2014]. Gabapentinoids (i.e., gabapentin and pregabalin) and tricyclic antidepressants (TCAs) have been found to be effective and generally well tolerated for PHN [Attal, 2010; Dubinsky, 2004; Edelsberg, 2011; Finnerup, 2015; Hempenstall, 2005]. Gabapentin is recommended as initial therapy for most patients with moderate or severe pain [Moore, 2011]. TCAs are recommended for patients who do not tolerate or respond to a gabapentinoid [Argoff, 2011; Chandra, 2006]. Conflicting evidences exist on the use of potent opioids (such as oxycodone) and tramadol in treating PHN [McNicol, 2013, Johnson, 2014; Finnerup, 2015]. Therefore opioids, including tramadol, should generally be considered as third-line drugs for treatment of PHN after consultation with a specialist and should be prescribed only with close monitoring.

Preventative option for the management of HZ

Zostavax (Merck), a high-titer preparation [14-fold higher potency than a varicella vaccine (*Varivax)*] of live attenuated VZV vaccine, was approved in the US and EU. In the EU, Zostavax is indicated for the prevention of HZ and HZ-related PHN in persons ≥ 50 YOA, but it is contraindicated in IC populations (e.g., malignancy, HIV infection or immunosuppressive therapy) [Zostavax, 2021]. *Zostavax* was removed from the US market in 2020 but continues to be marketed in other regions.

In Japan, another HZ vaccine containing the same live attenuated Oka VZV strain as *Zostavax* has been approved (*Biken*, The Research Foundation for Microbial Diseases of Osaka University).

In South Korea, *SkyZoster*, a shingles vaccine consisting of live attenuated VZV Oka strain, has been approved [SK Bioscience, 2020].

Herpes Zoster Vaccine, Live from Changchun, *BCHT* in China has been approved in 2023 [BCHT, 2023].

GSK's non-live and adjuvanted HZ/su vaccine was first approved on 13 October 2017 in Canada and has since been approved by regulatory agencies in more than 50 countries worldwide under the tradename *Shingrix.* It is intended for the prevention of HZ and HZ-related complications such as PHN in:

- Adults 50 YOA or older

- Adults 18 YOA or older at increased risk of HZ

Concomitant medication(s) in the target population

There are no specific medications/treatments typically or likely administered concomitantly that would impact the safety of *Shingrix*. However, the target population (i.e. adults 50 years of age and older, and adults 18 years of age and older at increased risk for HZ), might receive treatment for various co-morbid conditions.

In addition, the target population may be eligible for, or recommended to receive vaccinations other than *Shingrix* e.g., unadjuvanted seasonal influenza vaccine, 23-valent pneumococcal polysaccharide vaccine, 13-valent pneumococcal conjugate vaccine, reduced antigen diphtheria-tetanus-acellular pertussis vaccine or coronavirus disease vaccine.

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

Primary infection with VZV (chickenpox during childhood) is required prior to HZ onset. Once primary infection resolved, the virus establishes a latent infection in the dorsal-root, cranial nerve or the autonomous neuraxis ganglia [Mueller, 2008, Gilden, 2011, Cohen, 2013]. Reactivation of the virus (HZ) is often associated with age-related immunosenescence of VZV-CMI and iatrogenic or condition-related immunosuppression [CDC, 2018a].

Unilateral dermatomal distribution of a skin rash hallmarks the occurrence of HZ, although *zoster sine herpete* (dermatomal distribution of pain without skin rash) occurs in rare cases. HZ skin lesions progress through stages from red macules and papules to vesicles forming pustules and finally scabs. While less contagious than chickenpox lesions, HZ lesions can still spread to susceptible individuals through direct contact [CDC, 2018b]. The thoracic and lumbar dermatomes are the most commonly involved, but any dermatome can be affected. The dermatomal distribution of the rash corresponds to the neighboring ganglia involved in reactivation. A characteristic of the zoster rash is that it does not cross the midline, unlike other rashes.

Pain is the most common symptom of HZ, and most patients describe the pain as burning, throbbing or stabbing pain, the duration of pain increases with age. Approximately 75 % of patients have a prodromal pain around the affected dermatome, that precedes the rash by about 2 to 3 days; during which the pain could be misdiagnosed as another disease. [Dworkin, 2007a; Weaver, 2009].

Multiple episodes of HZ in the same individual can occur, approximately 1 to 6% of individuals will experience a second episode of HZ, three or more episodes in the same individual have been reported, but it is very rare. Recurrence is more common in immunocompromised individuals [Yawn, 2011; Weitzman, 2013; Shiraki, 2017].

HZ-related complications

Post-Herpetic Neuralgia (PHN) is the most frequent complication of HZ and it is a complex neuropathic pain due to nerve damage caused by the reactivation of VZV in the ganglia. The more conventional definition of PHN is dermatomal pain of clinically significant intensity, persisting at least 90 days after the appearance of the acute HZ [Johnson, 2010]. The incidence and prevalence of PHN vary by study depending on the definition and age groups studied, but the risk of developing PHN varies from 5% to more than 30%. [Kawai, 2014]. Prospective cohort studies demonstrated that approximately 30-50% of patients with PHN experience pain lasting for more than 1 year [Helgason, 2000; Watson, 2002; McKendrick, 2009; Bouhassira, 2012; Reda, 2013]. The major risk factors for PHN are older age, a greater acute pain and rash severity at HZ onset and an altered immune system [Drolet, 2010; Forbes, 2016; Le, 2019].

Other less frequent HZ complications include HZ ophthalmicus (HZO) which occurs in 10% to 15% of HZ patients [Johnson, 2014; Kawai, 2014]. HZO is defined as HZ involvement of the ophthalmic division of the fifth cranial nerve [Liesegang, 2008; Tran, 2016], it occurs more often in elderly patients. It is potentially sight-threatening and requires referral to an ophthalmologist and aggressive treatment, 50% of patients with untreated HZO develop ocular complications [Watson, 2017; Fan, 2018].

Other neurological complications such as VZV encephalitis, meningitis, and disseminated HZ [Dworkin, 2007a; Harpaz, 2008]. Ramsay Hunt syndrome rarely occurs (an estimated 5 cases per 100,000 patients) however it is a common cause of facial nerve paralysis [Adour, 1994; Uscategui, 2008]. An increased risk of stroke up to 3 months after a HZ episode has also been described [Kang, 2009; Langan, 2014].

Disseminated HZ is also a severe complication after HZ and can be cutaneous or visceral involvement [Rommelaere, 2012]. Lesions of disseminated HZ resembles that of varicella, and occurs rarely in immunocompetent individuals, but occurs in 15 to 33% of immunocompromised cases of HZ. Cutaneous disseminated HZ with multiple vesicular skin lesions occur in a generalized distribution, distant from the involved HZ dermatome [Watson, 2017]. Visceral dissemination is a life-threatening emergency. Visceral involvement can present as rapidly evolving severe, sudden onset of a syndrome of pneumonia, hepatitis or encephalitis.

Hospitalization associated with HZ

Rates of HZ-related hospitalization ranges from 2 to 25 per 100,000 PY in studies examining all ages, because of differing admission criteria in the different settings [Kawai, 2014]. Hospitalization rates with a primary diagnosis of HZ were estimated 4.1 per 100,000 inhabitants in France [Gonzalez Chiappe, 2010] and roughly 4.4 per 100,000 inhabitants in England [Brisson, 2003]. Hospitalization rates increase with age, with most cases occurring in adults ≥60 years of age [Esteban-Vasallo, 2016; Pham, 2019]. In Germany, hospitalization rate was about 45 per 100,000 PY in adults ≥50 years of age [Ultsch, 2011].

Mortality associated with HZ

Mortality associated with HZ is uncommon, rates range from 0.10 to 182.0 per 100,000 in the population with most of the deaths occurring in adults ≥ 85 years of age [Mahamud, 2012]. When considering HZ coded as primary and secondary diagnosis, the mortality rate was estimated to range from 0.11 to 0.29 per 100,000 persons in France [Gonzalez Chiappe, 2010] and 0.6 per 100,000 persons in Spain [Gil, 2009]. Risk factors for HZ-related mortality within 2 years of HZ diagnosis include age, race, ethnicity, and diagnosis of an IC condition [Ahn, 2019]. In persons with an IC condition such as end-stage renal disease, there is a significant increase in mortality with age [Ahn, 2019]. This trend towards higher HZ mortality rates in the older age groups also applies to the general population [Bricout, 2015].

SI.1.4 Important co-morbidities

The target populations which have been studied in clinical trials have reported a variety of comorbidities in frequencies generally similar to those observed in the general reflective population. In adults 50 years of age and older, the most frequent comorbidities reported are cardiovascular diseases, malignancies, pulmonary disease (including chronic obstructive pulmonary disease), hypertension, diabetes and autoimmune diseases. Subjects presenting such medical conditions were not excluded from clinical trials [Oostvogels, 2019]. Adverse events related to *Shingrix* were not found to be impacted by those comorbidities.

Given the diversity of underlying medical conditions and treatments in adults ≥18 YOA at increased risk of HZ, the generation of data in every patient population was not feasible, hence, a variety of IC conditions, from most to less severe impaired immune system, were selected to be included in the *Shingrix* clinical development program. In the IC program, 5 disease entities associated with IC conditions were the focus of randomized, placebo-controlled studies, all conducted in adults ≥18 YOA. These disease entities were hematopoietic stem cell transplant (HSCT) recipients, renal transplant recipients, as well as patients with solid tumors who were receiving chemotherapy, and patients with various hematologic malignancies (i.e., Multiple Myeloma, Non-Hodgkin T-cell Lymphoma, Hodgkin Lymphoma and Other Hematologic Malignancies) vaccinated during a cancer therapy course or after the full cancer therapy. In addition, 2 supportive Phase I/II studies enrolled adults ≥18 YOA with autologous HSCT and HIV infection.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

In nonclinical studies, IM administration of HZ/su (gE/AS01$_B$) led to a slight to mild transient inflammatory reaction at the injection site and draining lymph nodes. A few clinical, haematological and clinical chemistry parameters related to the local inflammation were transiently affected (changes in body temperature, C-reactive protein, fibrinogen, albumin/globulin ratio). These findings were fully or partially reversible after a 4-week treatment free period.

All findings were indicative of reactogenicity to the vaccine and consistent with the expected transient stimulation of the immune system.

In addition, no adverse treatment-related effects on male mating performance, male and female fertility, early embryonic development, pre- and post-natal survival, growth or development of the offspring up to day 25 of age were associated with repeated IM administrations of the gE/AS01$_B$ or AS01$_B$ alone.

There were no findings in the nonclinical testing that would warrant inclusion among the summary of safety concerns (Module SVII) and no nonclinical study is missing information (no inclusion in Module SVII.3).

Table 5 Key Safety findings (from nonclinical studies)

Key Safety findings (from nonclinical studies)	Relevance to human usage
Key issues identified from toxicity studies with HZ/su (gE/AS01B): **There were no issues identified; key findings included:** • Acute or repeated dose toxicity studies (2 single dose and 2 repeated dose studies, SC and IM administrations in rabbits): very slight to mild local inflammation at the injection site and draining lymph nodes, changes in body temperature and blood parameters such as C-reactive protein, fibrinogen, white blood cells, albumin/globulin ratio, indicative of an inflammatory reaction. These changes were completely or mostly reversed after 4 weeks. • One pre-, peri- and post-natal reproductive toxicity study in rat (IM administration: mild transient swelling at injection sites (dams). No adverse effect on embryo-fetal or pre- and post-natal survival, growth or development of the offspring. • One male fertility study in rats (IM administration): transient swelling at injection sites. No adverse effect on male mating performance and fertility, early embryonic development and male reproductive organ histology and function (semen parameters). • Genotoxicity studies are not required for vaccines. • Carcinogenicity studies are not required for vaccines.	There are no limitations for human usage based on results from non-clinical studies.

Key Safety findings (from nonclinical studies)	Relevance to human usage
Key issues identified from General Safety pharmacology studies with Hz/su (gE/AS01B): **There were no issues identified; key findings included:** • One safety pharmacology study in rats (IV administration): no influence on cardiovascular and respiratory parameters.	There are no limitations for human usage based on results from nonclinical studies.
Other toxicity-related information or data (as applicable) Toxicology studies have been performed with the adjuvant system AS01B and its components QS-21 and MPL. These studies provide supportive information. They include single and repeated dose toxicity, developmental and reproductive toxicity, male fertility (AS01B only) and genotoxicity studies. Safety pharmacology studies have been performed for AS01B and MPL. No safety signal was detected.	There are no limitations for human usage based on results from nonclinical studies.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

As of 12 October 2024, the cumulative number of subjects that have received *Shingrix* (either commercial or pediatric or exploratory formulation) in the GSK-sponsored interventional trials (completed and ongoing) is 38 159, among which 36 403 are subjects 50 YOA or older (hereafter, this population is referred to as older adults) and 1663 subjects who were IC due to disease or therapy 18 YOA or older (hereafter, this population is referred to as IC population).

The cumulative number of subjects and demographic characteristics from completed GSK-sponsored interventional clinical trials investigating *Shingrix* for the prevention of HZ or shingles is presented in Table 6, Table 7, and Table 8 .

Table 6 Cumulative Subject Exposure to *Shingrix* in Completed GSK Sponsored Interventional Studies by Age, Sex and Racial Group (Total vaccinated cohort-Overall)

	VZV-gE + AS01B N=36509		VZV-gE + AS01E N=178		VZV-gE explo N=619		Placebo N=21160		Active comparator N=2218		Total N=60684	
	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age in years at vaccination dose												
N with data	36509		178		619		21160		2218		60684	
Mean	67.5		63.6		72.0		66.6		62.8		67.0	
SD	10.5		10.7		6.6		10.5		8.5		10.5	
Median	69.0		64.0		72.0		69.0		62.0		69.0	
Minimum	18		24		51		18		49		18	
Maximum	100		95		94		97		94		100	
Age category												
Younger adults [18-49 Years]	479	1.3	6	3.4	0	0.0	433	2.0	4	0.2	922	1.5
Adults [50-59 Years]	9316	25.5	60	33.7	24	3.9	5891	27.8	875	39.4	16166	26.6
Adults [60-69 Years]	9001	24.7	61	34.3	134	21.6	4362	20.6	826	37.2	14384	23.7
Adults [70 Years or older]	17713	48.5	51	28.7	461	74.5	10474	49.5	513	23.1	29212	48.1
Gender												
MALE	15406	42.2	80	44.9	277	44.7	9012	42.6	974	43.9	25749	42.4
FEMALE	21103	57.8	98	55.1	342	55.3	12148	57.4	1244	56.1	34935	57.6
Geographic Ancestry												
AMERICAN INDIAN OR ALASKA NATIVE	46	0.1	2	1.1	0	0.0	18	0.1	6	0.3	72	0.1
ASIAN	7807	21.4	0	0.0	0	0.0	6160	29.1	41	1.8	14008	23.1
BLACK OR AFRICAN AMERICAN	574	1.6	4	2.2	1	0.2	236	1.1	92	4.1	907	1.5
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	7	0.0	0	0.0	0	0.0	7	0.0	0	0.0	14	0.0
WHITE	25461	69.7	170	95.5	617	99.7	12882	60.9	2047	92.3	41177	67.9
OTHER	2589	7.1	2	1.1	1	0.2	1838	8.7	29	1.3	4459	7.3
UNKNOWN	25	0.1	0	0.0	0	0.0	19	0.1	3	0.1	47	0.1

Data from completed trials as of 12 October 2024.
VZV-gE+AS01B=commercial formulation
VZV-gE+AS01E=pediatric formulation (half dose of commercial formulation adjuvant)
VZV-gE explo=exploratory formulation
Placebo=placebo control group
Active comparator=any non VZV gE nor placebo
N=number of subjects
n=number of subjects in a given category
Value=value of the considered parameter
N with data=number of subjects with documentation of the corresponding data
%=n / Number of subjects with available results x 100
SD=Standard deviation

Table 7 Cumulative Subject Exposure to *Shingrix* in Completed GSK Sponsored Interventional Studies by Age, Sex and Racial Group (Total vaccinated cohort-Older adults)

	VZV-gE + AS01B N=34922		VZV-gE + AS01E N=149		VZV-gE explo N=619		Placebo N=19600		Active comparator N=2218		Total N=57508	
	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age in years at vaccination dose												
N with data	34922		149		619		19600		2218		57508	
Mean	68.0		65.1		72.0		67.5		62.8		67.7	
SD	10.0		9.9		6.6		9.8		8.5		9.9	
Median	70.0		65.0		72.0		70.0		62.0		70.0	
Minimum	18		50		51		48		49		18	
Maximum	100		95		94		97		94		100	
Age category												
Younger adults [18-49Years]	37	0.1	0	0.0	0	0.0	10	0.1	4	0.2	51	0.1
Adults [50-59Years]	8809	25.2	50	33.6	24	3.9	5410	27.6	875	39.4	15168	26.4
Adults [60-69Years]	8482	24.3	49	32.9	134	21.6	3856	19.7	826	37.2	13347	23.2
Adults [70Years or older]	17594	50.4	50	33.6	461	74.5	10324	52.7	513	23.1	28942	50.3
Gender												
MALE	14409	41.3	60	40.3	277	44.7	8045	41.0	974	43.9	23765	41.3
FEMALE	20513	58.7	89	59.7	342	55.3	11555	59.0	1244	56.1	33743	58.7
Geographic Ancestry												
AMERICAN INDIAN OR ALASKA NATIVE	42	0.1	1	0.7	0	0.0	17	0.1	6	0.3	66	0.1
ASIAN	7565	21.7	0	0.0	0	0.0	5915	30.2	41	1.8	13521	23.5
BLACK OR AFRICAN AMERICAN	544	1.6	2	1.3	1	0.2	203	1.0	92	4.1	842	1.5
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	7	0.0	0	0.0	0	0.0	7	0.0	0	0.0	14	0.0
WHITE	24307	69.6	146	98.0	617	99.7	11767	60.0	2047	92.3	38884	67.6
OTHER	2452	7.0	0	0.0	1	0.2	1691	8.6	29	1.3	4173	7.3
UNKNOWN	5	0.0	0	0.0	0	0.0	0	0.0	3	0.1	8	0.0

Data from completed trials as of 12 October 2024.
VZV-gE+AS01B=commercial formulation
VZV-gE+AS01E=pediatric formulation (half dose of commercial formulation adjuvant)
VZV-gE explo=exploratory formulation
Placebo=placebo control group
Active comparator=any non VZV gE nor placebo
N=number of subjects
n=number of subjects in a given category
Value=value of the considered parameter
N with data=number of subjects with documentation of the corresponding data
%=n / Number of subjects with available results x 100
SD=Standard deviation

Table 8 Cumulative Subject Exposure to *Shingrix* in Completed GSK Sponsored Interventional Studies by Age, Sex and Racial Group (Total vaccinated cohort-Immunocompromised program, ≥18 years of age)

	VZV-gE + AS01B N=1587		VZV-gE + AS01E N=29		Placebo N=1560		Total N=3176	
	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age in years at vaccination dose								
N with data	1587		29		1560		3176	
Mean	54.8		56.0		55.4		55.1	
SD	12.5		11.4		12.4		12.4	
Median	57.0		58.0		57.0		57.0	
Minimum	18		24		18		18	
Maximum	85		70		87		87	
Age category								
Younger adults [18-49Years]	442	27.9	6	20.7	423	27.1	871	27.4
Adults [50-59Years]	507	31.9	10	34.5	481	30.8	998	31.4
Adults [60-69Years]	519	32.7	12	41.4	506	32.4	1037	32.7
Adults [70Years or older]	119	7.5	1	3.4	150	9.6	270	8.5
Gender								
MALE	997	62.8	20	69.0	967	62.0	1984	62.5
FEMALE	590	37.2	9	31.0	593	38.0	1192	37.5
Geographic Ancestry								
AMERICAN INDIAN OR ALASKA NATIVE	4	0.3	1	3.4	1	0.1	6	0.2
ASIAN	242	15.2	0	0.0	245	15.7	487	15.3
BLACK OR AFRICAN AMERICAN	30	1.9	2	6.9	33	2.1	65	2.0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0.0	0	0.0	0	0.0	0	0.0
WHITE	1154	72.7	24	82.8	1115	71.5	2293	72.2
OTHER	137	8.6	2	6.9	147	9.4	286	9.0
UNKNOWN	20	1.3	0	0.0	19	1.2	39	1.2

Data from completed trials as of 12 October 2024.
VZV-gE+AS01B=commercial formulation
VZV-gE+AS01E=pediatric formulation (half dose of commercial formulation adjuvant)
Placebo=placebo control group
Active comparator=any non VZV gE nor placebo
N=number of subjects
n=number of subjects in a given category
Value=value of the considered parameter
N with data=number of subjects with documentation of the corresponding data
%=n / Number of subjects with available results x 100
SD=Standard deviation

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 9 Exclusion criteria

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine	*Shingrix* should not be administered to subjects with known hypersensitivity to any component of the vaccine. Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following administration of the vaccine.	No	Included in SmPC Section 4.3, Contraindications
Pregnancy or breastfeeding	Animal studies performed with *Shingrix* administered to female rats do not indicate any harmful effects with respect to pregnancy, embryonal/fetal development, parturition or post-natal development; however, *Shingrix* has not been studied prospectively in pregnant or lactating women. Pregnant and breastfeeding females have been excluded from all clinical trials with *Shingrix* and contraceptive measures in women of childbearing potential were to be implemented in order to prevent pregnancies. 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.	No	Included in SmPC Section 4.6, Fertility, pregnancy and lactation.
Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within six months prior to the first	In the context of a clinical trial, for these subjects, a protective immune response and efficacy may not be obtained further complicating interpretation of the results.	No	Immunocompromised people are at high risk for HZ and may therefore benefit from vaccination. In addition, because *Shingrix* is a subunit

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
vaccine dose (applicable to older adult program).			vaccine, it is not anticipated that the vaccine itself may cause HZ. Several studies evaluating the administration of *Shingrix* in adults 18 YOA with immunocompromising conditions and immunosuppressive medications have been completed
Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or immunosuppressive/cytotoxic therapy (applicable to older adult program).	In the context of a clinical trial, for these subjects, a protective immune response and efficacy may not be obtained further complicating interpretation of the results.	No	Immunocompromised people are at high risk for HZ and may therefore benefit from vaccination. In addition, because *Shingrix* is a subunit vaccine, there is no risk that the vaccine itself may cause HZ. Several studies evaluating the administration of *Shingrix* in adults 18 YOA with immunocompromising conditions and immunosuppressive medications have been completed
Administration of immunoglobulins and/or any blood products within 3 months preceding the first vaccine dose or administration during the study period.	Use of these products could impair GSK's ability to accurately assess subjects' immune status (baseline and post-vaccination).	No	There is no reason to believe that administration of immunoglobulins would influence vaccine efficacy or safety.
History of HZ	Prior HZ may have impacted subjects' risk to develop HZ and could have impaired GSK's ability to accurately assess vaccine efficacy	No, previously included as an important potential risk	An uncontrolled phase III trial conducted in 96 adults 50 years of age and older with a history of HZ indicates that the safety and immunogenicity profile of *Shingrix* appears to be generally consistent

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			to that observed in other clinical studies conducted in a population with no history of HZ [Godeaux 2017]. A 2nd study, a controlled phase III study (ZOSTER 062) in this population was completed and did not show any safety concerns.
Previous vaccination against HZ or varicella.	Such previous vaccinations may have impacted subjects' risk to develop HZ and could have impaired GSK's ability to accurately assess vaccine efficacy	No	A clinical trial in subjects previously vaccinated against HZ is completed [Grupping 2017]. Individuals previously vaccinated against HZ can be given *Shingrix*; wording is included in SmPC section 4.2 Posology and method of administration.
Administration of a live vaccine 30 days before the first dose to the last blood sampling, or, administration of a non-replicating vaccine within 8 days prior to or within 14 days after either dose of *Shingrix*.	These products could influence the subject's immune response to the vaccine and could affect the accurate assessment of *Shingrix*-related AEs.	No	Several studies evaluating the co-administration of *Shingrix* with other vaccines commonly used in the target population of older adults have been completed.
Acute disease	This exclusion criterion avoids causing diagnostic confusion between manifestations of the underlying illness and possible adverse effects of vaccination or superimposing adverse effects of the vaccine on the underlying illness.	No	The safety and efficacy of vaccinating persons who have mild illnesses have been documented [Kroger, 2011]. Administration of *Shingrix* should be postponed in subjects suffering from acute severe febrile illness.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			However, the presence of a minor infection, such as a cold should not result in the deferral of vaccination. Included in SmPC section 4.4 Special warnings and precautions for use.
Any condition which, in the judgment of the investigator would make intramuscular injection unsafe.	The intramuscular route of administration of a vaccine could cause adverse effects in people with thrombocytopenia or any coagulation disorder since bleeding may occur.	No	Included in SmPC section 4.4 Special warnings and precautions for use.

SIV.2 Limitations to detect adverse reactions in clinical trial development program

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Table 10 Limitations to detect adverse reactions in clinical trial development program

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	Over 38,000 subjects as of 18 years of age were vaccinated with at least one dose of *Shingrix* (or HZ/su in different formulations) in the whole clinical development program from studies completed to date.	Within the Zoster clinical development program, adverse events associated with exposure to vaccine in over 17 000 subjects comprising the integrated safety population have been evaluated. ADRs occurring at a frequency of less than 0.0028% (1/38 000 subjects) may only be observed when a larger population is exposed.
Due to prolonged exposure	Not applicable	The vaccine is delivered in two doses over maximum six months and is not considered as prolonged exposure
Due to cumulative effects	Not applicable	No cumulative exposure or specific organ toxicity has been observed with *Shingrix*.
Which have a long latency	Potential immune-mediated disorders (pIMDs) may have a long latency from vaccine exposure to disease onset, therefore collection of pIMDs in GSK clinical trials with vaccines containing novel adjuvants is typically set for at least one year after the last vaccine dose, which is a reasonable maximum theoretical risk interval for these diseases.	One may assume that the development of autoimmunity (if a causal association between the event and vaccination exists) is similar to the classical time frame of several weeks suggested for the onset of post-infectious autoimmune phenomena. The risk becomes very low several months following the last vaccine dose received [Tavares Da Silva, 2013].

SIV.3 Limitations in respect to populations typically under-represented in clinical development program

Table 11 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	Excluded from clinical trials within the clinical development program. A small number of subjects did become pregnant during some clinical trials.
Breastfeeding women	Excluded from clinical trials within the clinical development program.
Patients with relevant comorbidities: I. Patients with hepatic impairment II. Patients with renal impairment III. Patients with cardiovascular impairment IV. Patients with a disease severity different from inclusion criteria in clinical trials V. Immunocompromised patients	Not specifically assessed. The target population which has been studied in clinical trials has reported a variety of comorbidities in frequencies that are generally comparable to those observed in the general reflective population of this age (≥50 years). In adults 50 years of age and older, the most frequent comorbidities reported are cardiovascular diseases, malignancies, pulmonary disease (including chronic obstructive pulmonary disease), hypertension, diabetes and various autoimmune diseases. Subjects presenting such medical conditions were not excluded from clinical trials. Adverse events related to *Shingrix* were not found to be impacted by those comorbidities [Oostvogels, 2019]. Immunocompromised subjects with active disease under treatment were excluded from clinical trials in the older adult program. A clinical development program in IC adults is now completed. The following conditions known to be associated with a severe impairment of the immune system were selected as part of the IC clinical development plan (CDP) and studied in 1 Phase II/III & 3 Phase III trials: autologous HSCT recipients vaccinated post-transplant, renal transplant recipients on chronic immunosuppressive treatment at the time of vaccination, patients with solid tumors who were undergoing chemotherapy, and patients with hematologic malignancies vaccinated during a cancer therapy course or after the full cancer therapy. In addition, 2 supportive Phase I/II studies enrolled adults ≥18 YOA with autologous HSCT and HIV infection.
Population with relevant different ethnic origin	Not specifically assessed.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Other	Not applicable

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

On 25 January 2018, *Shingrix* received a positive opinion from the CHMP through the centralized procedure. Marketing authorization is currently valid throughout the European Economic Area since 21 March 2018.

SV.1 Post-authorization exposure

Changes to the post-marketing exposure do not alter considerations on the risk evaluation for *Shingrix*.

SV.1.1 Method used to calculate exposure

The exact number of individuals vaccinated with *Shingrix* is unknown due to limited availability and heterogeneity of data sources between and within countries. Factors such as multiple national immunization schedules, specific mass vaccination campaigns, incidence of the disease, catch-up efforts, and outbreak containment measures complicate the collection of precise exposure data. Consequently, the exposure estimate is approximated by the number of doses distributed, which is the only worldwide data available regarding subject exposure for a vaccine in a post-approval setting.

It is important to note that the sales database from which data are retrieved is an in-house 'living' database and is subject to updates and corrections depending on information provided by GSK local country subsidiaries (e.g. vaccine doses may be returned by subsidiaries to the central warehouse). These constant updates may result in discrepancies between consecutive queries of the sales database. It is important to note that the distribution data is available per complete month and there is an average time lag of 2 months between the actual distribution to a country and its recording in the database. To minimize the risk of inaccuracy and to better reflect the exposure data the distribution data are retrieved with data lock point (DLP) minus 2 months (07 January 2025).

SV.1.2 Exposure

Since launch until 07 March 2025, it is estimated that 152 206 480 doses of *Shingrix* have been distributed. As vaccination with *Shingrix* could vary between one and two doses per subject depending on the compliance with the vaccination schedule, post-approval exposure to *Shingrix* since launch is estimated to be between 76 103 240 and 152 206 480 individuals.

Table 12 Exposure (dose)

EU countries	**28 064 982**
Non-EU countries	**124 141 498**

For *Shingrix*, information on the actual use in special populations is not available to GSK. Assuming that sales distribution in individuals with immunocompromising conditions are in the same proportion as the number of spontaneous reports (4.9% of the spontaneous reports involved individuals with immunocompromising conditions), it is estimated that

exposure in individuals with immunocompromising conditions is between 3 729 059 and 7 458 118 individuals.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

No potential for illegal use of the vaccine has been identified.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

The list of risks considered important for inclusion on the list of safety concerns in the initial RMP are provided below.

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination • Virus reactivation in individuals with a history of Herpes Zoster
Missing information	• Long-term efficacy and assessment of the need for additional doses in adults 50 years of age and older. • Long-term immunogenicity in adults 50 years of age and older. • Use of *Shingrix* in frail adults 50 years of age or older • Use of *Shingrix* in immunocompromised adults • Use of Shingrix in adults with pre-existing pIMD • Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complications

SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Table 13 Summary of changes to the list of safety concerns

EU-RMP version number	Changes to the list of safety concerns
2.2	Removal of the missing information 'Inadvertent use of *Shingrix* during pregnancy'; rephrase of the potential risk to 'Virus reactivation in immunocompetent individuals with a history of HZ'
3.0	Removal of the missing information 'Use of *Shingrix* in adults with pre-existing pIMD' and of the category 3 Post Approval Commitment MEA-FSR-008 on ZOSTER-069
5.0	Removal of 'Use of *Shingrix* in frail adults 50 years of age or older' from list of missing information
6.0	Addition of Guillain-Barré syndrome (GBS) as standalone important potential risk
9.1	Removal of 'Virus reactivation in individuals with a history of Herpes Zoster' from list of important potential risks
12.2	Reclassification of Guillain-Barré syndrome (GBS) from important potential risk to important identified risk

The risk of "Guillain-Barré syndrome (GBS)", previously classified as an important potential risk, has been reclassified as an important identified risk.

GBS results from the PASS EPI-ZOSTER-032 VS US DB, to evaluate the safety of *Shingrix* in adults ≥65 years of age in the US, showed a statistically significant increased risk of GBS post any dose within the 42-day risk window (RR=3.15 [95% CI: 1.82-5.68]). Please refer to "Important Identified Risk: Guillain-Barré syndrome (GBS)" under Part II: Module SVII.3.1 for a summary of the study and results.

Further to the results from the EPI-ZOSTER-032 study, a comprehensive evaluation of all available data was conducted and the results are summarized below:

- Results of EPI-ZOSTER-032 are consistent with those observed in another study [Goud, 2021], which also analyzed the Medicare population (≥65 years of age) and used a similar methodology.
- Acknowledging the known limitations of spontaneous reports (including underreporting, biased reporting, and incomplete documentation), there has however been an increasing trend in the reporting of GBS spontaneous reports over time and the analysis of GBS cases from spontaneous reporting identified a number of cases (n=32) where TTO was within the risk window (up to 42 days) and no other confounding factors were documented.
- The available GSK clinical trial data from individuals vaccinated with *Shingrix* do not suggest an increased occurrence of GBS following vaccination. However, cautious interpretation of these results is warranted because the clinical trials were not designed to evaluate an association between vaccination and rare diseases such as GBS.
- The observed number of GBS cases following *Shingrix* vaccination is below the expected for several plausible scenarios of background incidence rate and reported fraction. It should be noted that Observed/Expected (O/E) analyses are signal strengthening tools aiming to support signal evaluation and that it is only one method

among other data sources and other quantitative methods available from the pharmacovigilance toolkit. O/E analyses are not suited to perform specific hypothesis testing or to measure strength of associations between adverse events.

Based on the totality of available evidence, GBS has been reclassified from an important potential risk to an important identified risk.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk:

Important identified risk: Guillain-Barré syndrome (GBS)	
Potential mechanisms	GBS is considered an immune-mediated disorder resulting from generation of autoimmune antibodies and/or inflammatory cells which cross-react with epitopes on peripheral nerves and roots, leading to demyelination or axonal damage or both [Sejvar, 2011]. Although the underlying etiology and pathophysiology of GBS are not completely understood, it is believed that immune stimulation plays a role in its pathogenesis [Sejvar, 2011].
Evidence source and strength of evidence	GBS results from the PASS EPI-ZOSTER-032 VS US DB, to evaluate the safety of *Shingrix* in adults ≥65 years of age in the US, showed a statistically significant increased risk of GBS post any dose within the 42-day risk window (RR=3.15 [95% CI: 1.82 - 5.68]). A summary of the study and the results are provided below: **EPI-ZOSTER-032** The study EPI-ZOSTER-032 VS US DB is designed to address whether there is an increased risk of new-onset (incidence) GBS within 42 days (6 weeks) following at least 1 dose of *Shingrix* vaccination in US adults ≥65 years of age. Using the CMS Chronic Condition Warehouse Medicare database, the study employs self-controlled risk interval design, whereby each individual serves as their own control (Days 43-84). A total of 75 Medicare beneficiaries who met the inclusion criteria were included in the GBS analytic cohort. The mean age was 75.37 (±6.98) years, and 50.67% were females. Twenty-two received both doses of *Shingrix* while 53 received only 1 dose. Some of the commonly reported comorbidities included diabetes mellitus (16, 21.3%), chronic kidney disease (15, 20%), and chronic lung disease (12, 16%). The data were analyzed both descriptively which shows baseline demographic and health characteristics, and inferential analysis shows the risk of incident GBS in risk window relative to control using a conditional Poisson regression. The results showed 75 incident GBS cases post any dose, of which 57 (76%) cases were reported after Dose 1 and 18 after Dose 2. Of the 75 incident GBS cases, 57 were reported within the 42-day risk window while 18 were reported in the Control window (43-84 days). The peak incidence was observed within 14 days post any dose in 25 (44%) cases and 32 cases

Important identified risk: Guillain-Barré syndrome (GBS)	
	occurred 15-42 days after exposure. The distribution of cases by *Shingrix* dose could not be displayed due to masking criteria (as per Medicare data use agreement, data cells <11 cannot be disclosed), even when aggregating the days. The primary analysis showed a statistically significant increased risk of GBS post any dose within the 42-day risk window (RR = 3.15 [95% CI: 1.82 - 5.68]) and AR per million doses (6.59 [95% CI: 4.35 – 7.96]). A similar trend was observed for secondary analysis when using the Fixed-3 week (RR = 3.56 [95% CI: 1.69–8.65]; AR = 6.95 [95% CI: 3.94 – 8.54]) or 6-week Control window (RR = 3.17 [95% CI: 1.84–5.72]; AR = 6.61 [95% CI: 4.41 – 7.97]). Dose specific sensitivity analysis found an increased risk of GBS following Dose 1 (RR = 5.33 [95% CI: 2.59 – 12.36]; AR = 11.83 [95% CI: 8.94-13.38]) but not Dose 2. Seasonality adjusted and COVID-19 sensitivity analyses were also consistent with the primary analysis. Additional post-hoc analyses, such as excluding participants with baseline Gastrointestinal / Respiratory infection and those who received concomitant vaccinations (e.g., Influenza, Pneumococcal, Tdap) ≤42 days prior to *Shingrix* vaccination; PPV adjustment assuming 50% PPV age stratification showed consistent results though the risk was attenuated in adults aged 65 to 74 years as compared to the primary analysis. These results are consistent with the risk of GBS as observed in a study by Goud, 2021 (RR = 2.84 [95% CI: 1.53 – 5.27]; AR per million doses = 3.13 (95% CI: 0.62 - 5.64) after extended study period).
Characterization of the risk	**Frequency** In clinical trials, overall, GBS cases were reported at comparable rates regardless of treatment group. In post-marketing setting (DLP: 20 August 2024): Cumulatively since launch, reporting rate of GBS is 0.26 cases per 100 000 doses distributed. Observed/Expected analysis showed that the number of GBS cases following *Shingrix* vaccination is below the expected for several plausible scenarios of background incidence rate and reported fraction. **Reversibility** Overall, GBS is generally associated with eventual favorable outcome, with most patients experiencing clinical improvement over weeks to months, although anecdotal evidence suggests that outcomes may be less favorable in resource-poor settings with limited access to treatment and intensive care. In infants and children, recovery is more rapid and tends to be complete, with fatalities rare. Elderly patients have a worse prognosis. Overall, approximately 5% to 15% of patients die, and continued disability after 1 year has been estimated to be seen among 20% of patients. Complete recovery is common in the remainder, although persistent mild weakness, numbness, pain, and fatigue may be reported [Sejvar, 2011].
Risk factors and risk groups	Incidence of GBS increases with age by 20% for every decade of age, from 0.90 per 100 000 person-years in adults aged 20-29 years to 2.66 per 100 000 person-years in adults 80-89 years [Sejvar, 2011].GBS is an immune-mediated polyneuropathy which can occur

Important identified risk: Guillain-Barré syndrome (GBS)	
	naturally in the adult population. Approximately two-thirds of GBS cases occur several days or weeks after an apparent infectious illness, commonly a gastrointestinal illness or upper respiratory tract infection. Campylobacter enteritis, influenza, cytomegalovirus, Epstein-Barr virus, HIV, chikungunya, Zika virus, and Mycoplasma pneumoniae have been implicated to be the trigger. Malignancies and surgical procedures also have been suggested to increase the risk of GBS [Chen, 2020].
Preventability	No preventability measures have been identified.
Impact on the risk-benefit balance of the product	In the EPI-ZOSTER-032 study, the AR of GBS per million doses after any dose was estimated to be 6.59 (95% CI: 4.35 – 7.96), while the AR estimated in the US Medicare post-marketing study [Goud, 2021] is 3.13 excess cases of GBS per million doses administered, in the claims database. Considering the prevalence of shingles and shingles complications, the risk of GBS is low and is outweighed by the benefit of shingles prevention following *Shingrix* vaccination. The anticipated benefit/risk balance of *Shingrix* vaccination remains favorable.
Public health impact	The potential public health impact related to this potential risk is thought to be limited. In 2 post-marketing observational studies in the US, among individuals aged 65 years or older, an increased risk of GBS (estimated 3 to 7 excess cases per million doses administered) was observed during the 42 days following any dose of Shingrix. In further analyses, the increased risk was observed following the first dose of Shingrix (estimated 6 to 12 excess cases of GBS per million doses administered), but no increased risk was observed following the second dose.

Important Potential Risk:

Important potential risk: Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination	
Potential mechanisms	Because adjuvants act directly as immune-stimulants there is a theoretical possibility that adjuvanted vaccines may induce an abnormal immune response that could trigger the onset of immune mediated diseases in susceptible individuals [Di Pasquale, 2015].
Evidence source and strength of evidence	pIMDs are a subset of adverse events that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune aetiology. pIMDs are considered as a theoretical risk for all vaccines containing Adjuvant Systems (i.e. adjuvant combinations). In addition to genetic factors, environmental triggers (in particular, viruses, bacteria and other infectious pathogens) could play a major role in the development of pIMDs [Wraith, 2003]. This has stimulated the debate as to whether such diseases might also be triggered by vaccines, particularly based on their possible effects on the regulation of the immune system and the potential (yet theoretical) concern that they may induce unwanted immune processes in susceptible individuals. Case reports of autoimmune diseases temporally associated with the administration of vaccines (both adjuvanted and non- adjuvanted) have been described in the scientific literature. Most of these reports refer to vaccines targeting viral illnesses. Proposed mechanisms by which vaccines might induce autoimmune diseases are frequently extrapolated from the known capacity of the infectious agents that the vaccine targets [Tavares Da Silva, 2013].
Characterization of the risk	**Frequency** In clinical trials, there were no clinically significant imbalances with regard to the proportions of subjects reporting pIMDs overall and no substantial differences were noted between treatment groups for subjects reporting pIMDs by specific Preferred Term (PT) or group of PTs within the same medical context. In post-marketing setting (DLP: 12 October 2024): Since launch of *Shingrix* reporting rate of pIMDs is 1.55 cases per 100 000 doses distributed. Overall, the most frequently reported events were GBS (reporting rate=0.26), facial paralysis (reporting rate=0.21), RA (reporting rate=0.07), and polymyalgia rheumatica (reporting rate=0.05). Review of individual spontaneous reports of pIMDs do not suggest a safety concern. Of the cases that reported a pIMD in the patient's medical history, reporting rate of cases with new onset of a different pIMD is 0.16 and reporting rate of cases with possible flare/exacerbation of the pre-existing pIMDs is 0.19. **Reversibility** The current approach to autoimmune diseases has significantly improved the outcome and has raised a new hope for a possible remission. Immunosuppression is the mainstay of therapy currently. The current strategy of immunosuppression though helps in reducing symptoms but the overall impact on the disease is not effective, especially in inducing remission or a long-lasting cure. The commonly used role model of therapies of infectious disease, oncology, and metabolic disease are not applicable in to in the management of autoimmune diseases. Autoimmune diseases being an immune dysregulation, with multistep aberration and being a dynamic disease

Important potential risk: Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination	
	the current approach of managing autoimmune diseases as a chronic disease have not achieved the much-desired remission. Thus, a treatment protocol should be based on biomarkers and other immunological markers in a stepwise manner to restore a homeostatic nonaggressive immune system. This is a possible target since spontaneous remission is well documented in autoimmune diseases. A systematic approach to design a personalized treatment to autoimmune diseases should help to achieve this goal (Chandrashekara, 2012). Naturally occurring autoimmune diseases are multi-etiological conditions with multiple risk factors, including genetic predisposition. All ages are affected with onset from childhood to late adulthood, as well as all racial, ethnic and socioeconomic groups. No specific trend in terms of groups or risks factors has been identified following *Shingrix* administration.
Risk factors and risk groups	Naturally occurring autoimmune diseases are multi-etiological conditions with multiple risk factors, including genetic predisposition. All ages are affected with onset from childhood to late adulthood, as well as all racial, ethnic and socioeconomic groups. No specific trend in terms of groups or risks factors has been identified in *Shingrix*.
Preventability	No preventability measures have been identified.
Impact on the risk-benefit balance of the product	The severity depends on the nature of the pIMDs. Most of the pathologies are chronic and can be disabling.
Public health impact	The public health impact cannot be assessed as potential immune diseases are a theoretical risk.

SVII.3.2 Presentation of the missing information

Missing information 1: Long-term efficacy and assessment of the need for additional doses in adults 18 years of age and older

Evidence Source:

At the time of initial marketing authorization, *Shingrix* efficacy data against HZ was shown to be maintained up to 4 years post-vaccination in adults 50 YOA or older. In ZOSTER-002, the overall HZ VE in autologous HSCT recipients ≥18 YOA was 68.17% (95% CI: 55.56%, 77.53%) with a LL of the 95% CI above 0% over a median follow-up time of 21 months. The post-hoc efficacy calculations in the mTVC of ZOSTER-039 in patients with hematologic malignancies are in line with the VE calculated for autologous HSCT patients in ZOSTER-002. However, it is not known how long after this time the vaccine efficacy will persist. It is also not known if, in case of waning efficacy, the addition of 1 or 2 additional doses of *Shingrix* will be able to maintain protection by boosting the immune response of previously vaccinated individuals.

A long-term efficacy study was conducted to assess protection of the vaccine against HZ up to 11 years after initial vaccination (ZOSTER-049), it included a re-vaccination sub-cohort receiving the vaccine 5 years post initial vaccination. The study is an extension of the two pivotal studies in subjects 50 and 70 YOA and above (ZOSTER-006 and ZOSTER-022 respectively). The results indicated a persistent and robust VE against HZ, and a robust immune response to the vaccine in individuals aged ≥50 YOA, approximately 11 years after initial vaccination. No safety concern was identified.

- Over the duration of ZOSTER-049 study (primary objective) and from 1 month post-Dose 2 of ZOSTER-006/022 studies until the end of ZOSTER-049 study, overall VE against HZ was 79.77% (95% CI: 73.72-84.61) and 87.73% (95% CI: 84.89-90.12), respectively.
- Over each year of follow-up from 1 month post-Dose 2 in the ZOSTER-006/022 studies until the end of ZOSTER-049 study, overall VE against HZ was high and was at 82.00% (95% CI: 63.03-92.22) at Year 11.

In addition, humoral and cellular immune responses remained above pre-vaccination levels:

- Geometric mean concentrations of anti-gE antibody remained high across years post primary vaccination until the end of the study. The vaccine response rate (VRR) for anti-gE antibody remained above 60% and mean geometric increase above 5.60 from Year 5 to Year 12 after primary vaccination.
- The median frequency of gE-specific CD4[2+] T-cells remained above pre-vaccination levels and the VRR remained above 44.8 % from Year 6 until the end of the study.

In study ZOSTER-060 [Hastie, 2021], a vaccine immune response persistence study in adults ≥60 YOA at primary vaccination, demonstrated that 10 years after initial vaccination, humoral and CMI responses were approximately 6-fold and 3.5-fold over pre-vaccination levels, respectively. Modeling using all data up to 10 years (Month 120) after

the primary vaccination series predicted that the immune responses would remain above the pre-vaccination level at least 20 years after vaccination. The study also demonstrated that a second course of vaccination, 10 years after the initial course in adults 60 YOA or older, showed that *Shingrix* elicited a strong immune response after the first revaccination dose. No further increase in the immune response was observed after the second dose of the re-vaccination course. One year after the second re-vaccination dose, both cell-mediated and humoral immune responses persisted above the pre-re-vaccination (Month 120) and pre-vaccination level (Month 0).

Immunogenicity data from studies ZOSTER-060 and ZOSTER-049, and efficacy data from study ZOSTER-049, where vaccine efficacy remained high at Year 11 follow-up, suggest that a need for booster dose is not established for now.

For the IC population (18-49 YOA), long-term follow-up studies of vaccine efficacy are not planned, since such extension studies would not provide meaningful results, as the immune status of the individuals involved in IC studies ZOSTER-002, ZOSTER-039 and ZOSTER-028 evolves over time with different outcomes (partial or complete remission, relapse or progression of the underlying disease). In addition, the subjects included in these studies have been evaluated when they were at their highest risk of HZ.

ZOSTER-041 study was the only study in the IC program with an IC population of relatively stable immune status (i.e. renal transplant recipients under chronic IS therapy), and where assessing long-term immunogenicity is considered pertinent. Therefore, the company completed an exploratory long-term follow-up of the ZOSTER-041 study population (i.e. ZOSTER- 073); refer to Missing information 2 for details of the results of this study.

Anticipated risk/consequence of the missing information:

If long term efficacy and assessment for additional doses is not evaluated, patients might potentially not be sufficiently protected against HZ and HZ-related complications. Data on this missing information was obtained from long-term study ZOSTER-049 and continues to be addressed with the follow-up long-term study ZOSTER-101. A vaccine effectiveness study (EPI-ZOSTER-031) in adults 50 YOA or older is ongoing.

Missing information 2: Long-term immunogenicity in adults 18 years of age and older

Evidence Source:

At the time of the initial marketing authorization, the vaccine-induced immune response (humoral and CMI) was shown to persist for at least 72 months post Dose 1, following a 0, 2- month vaccination schedule. Data from a long-term follow-up study assessing immune response to initial vaccination (ZOSTER-060) shows that the humoral and CMI immune responses to gE elicited by 2 doses of *Shingrix* administered in adults ≥60 YOA are sustained up to 10 years, at levels above the pre-vaccination levels and within the same range as the plateau levels reached at approximately 4 years after vaccination.

In study ZOSTER-049 (follow-up period of approximately 11 years after initial vaccination of 2 doses of *Shingrix* in adults ≥50 YOA) the humoral and CMI responses remained above pre-vaccination levels. An exploratory follow-up study (ZOSTER-073) in a small subset of renal transplant recipients ≥18 YOA from ZOSTER-041, under lifelong immunosuppressive therapy has also been completed.

ZOSTER-073 was a 'Long-term immunogenicity study of Herpes Zoster subunit vaccine and immunogenicity and safety assessment of revaccination with two additional doses in adults with renal transplant from study ZOSTER-041'. Long-term immunogenicity data generated in study ZOSTER-073 indicated that in adults with renal transplant from study ZOSTER-041, vaccination with HZ/su provided apparently stable immune responses, both humoral and cell-mediated, that remain above pre-primary vaccination levels at study Day 1, Month 12, and Month 24, 4-8 years post-primary vaccination. A summary of the study results pertaining to long-term immunogenicity are provided below:

ZOSTER-073

Persistence of immunogenicity was evaluated in a long-term follow-up phase IIIb, open-label study in 68 renal transplant recipients aged ≥ 18 years on chronic immunosuppressive therapy from Zoster-041. The Zoster-073 study started 4 to 6 years post-vaccination in Zoster-041 depending on the participant. In the enrolled set, at the time of enrollment in ZOSTER-073, the majority of the participants were aged ≥50 years (79.4%), and most of the participants were male (67.6%).

Humoral immune response persisted at consistent low levels above pre-primary vaccination from Day 1 through Months 12 and 24, approximately 4-8 years post-dose 2 of primary vaccination series, with:

- Mean geometric increase between 2 and 3
- Geometric mean antibody concentration between 3000 and 4000 mIU/mL. All long-term follow-up GMC were higher than pre-primary vaccination of 1313.3 mIU/mL.
- Seropositivity ≥98%. All long-term follow-up seropositivity percentages were higher than pre-primary vaccination of 95.6%.
- Vaccine Response Rate ≥30%
- Median fold increase from pre-vaccination between 2 and 4
- Distribution of fold increase from pre-vaccination >50% of participants over two-fold

Similar trends in response to Humoral immunity (HI) were seen in long-term Cell-mediated immunity (CMI) responses. The sample size was smaller; however, CMI response persisted at consistent levels above pre-primary vaccination from Day 1 through Months 12 and 24, approximately 4-8 years post-dose 2 of primary vaccination series, with:

- Median frequency between 299 and 711 CD4[2+] T-cells
- All long-term follow-up median frequency CD4[2+] T-cells were higher than pre-primary vaccination of 31.0 CD4[2+] T-cells.
- Vaccine Response Rates >40%.

- Median fold increase over pre-primary vaccination >4
- Distribution of fold increase from pre-primary vaccination: >72% of participants over 2-fold

The long-term safety profile of *Shingrix* in renal transplant participants remained consistent with the known safety profile of *Shingrix*. No new AEs were identified.

This missing information will be re-evaluated following the completion of study ZOSTER-101.

Anticipated risk/consequence of the missing information: No anticipated risk has been identified for this missing information.

Missing information 3: Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complications

Evidence Source:

In the real world setting, vaccine effectiveness was high and the second dose administered beyond the recommended 6 month interval does not seem to impact vaccine effectiveness [Izurieta, 2021; Sun, 2021a; Sun, 2021b]. Regarding post-marketing exposure to *Shingrix*, the evaluation of the confirmed and suspected vaccination failure cases and the case of HZ complication reported since launch did not provide evidence of a safety concern regarding effectiveness of the vaccine and risk of complications.

Anticipated risk/consequence of the missing information

If vaccine effectiveness is not guaranteed, vaccinees may not be sufficiently protected against HZ and other HZ-related complications. A study to evaluate vaccine effectiveness in adults 50 YOA or older is ongoing (EPI-ZOSTER-031).

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 14 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Guillain-Barré syndrome (GBS)
Important potential risks	• Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination
Missing information	• Long-term efficacy and assessment of the need for additional doses in adults 18 years of age and older. • Long-term immunogenicity in adults 18 years of age and older. • Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complications

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORIZATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are required:

Specific follow-up questionnaires for:

Risk of pIMDs and Guillain-Barré Syndrome following *Shingrix* vaccination:

Follow-up questionnaires are used as part of GSK routine surveillance system when following up spontaneous reports after vaccination with *Shingrix* of the following events of interest:

- Autoimmune thyroiditis
- Gout
- Guillain-Barré Syndrome (GBS)
- Idiopathic Thrombocytopenia
- Inflammatory (non-infective) ocular disease
- Inflammatory bowel diseases
- Leukocytoclastic vasculitis
- Multiple Sclerosis
- Optic ischemic neuropathy (arteritic and non-arteritic)
- Optic neuritis
- Polymyalgia rheumatica
- Psoriasis
- Rheumatoid arthritis
- Still's disease (adult onset)
- Temporal arteritis

Lack of efficacy

These questionnaires will help gathering more complete clinical information systematically for any reported cases and will therefore allow to support eventual signal characterization activities for these events.

Other forms of routine pharmacovigilance activities for the risk of pIMDs (including Guillain-Barré Syndrome) following *Shingrix* vaccination

GSK has generated background incidence rates for pre-selected pIMD events listed below that could possibly occur in coincident temporal association with *Shingrix* vaccination, considering the population targeted by the vaccine. In case a signal arises for these or other pIMDs, appropriate background rates will be timely generated and/or updated to support signal characterization activities, such as observed-to-expected analyses.

- Autoimmune thyroiditis
- Gout
- Idiopathic Thrombocytopenia
- Inflammatory bowel diseases
- Leukocystoclastic vasculitis
- Multiple Sclerosis
- Optic ischemic neuropathy (arteritic and non-arteritic)
- Optic neuritis
- Polymyalgia rheumatica
- Psoriasis
- Rheumatoid arthritis
- Still's disease (adult onset)
- Temporal arteritis

In each PSUR of *Shingrix*, a cumulative review of all pIMDs and GBS will also be presented.

These activities will allow to monitor the safety concern, and to evaluate signals in a timely fashion.

III.2 Additional pharmacovigilance activities

Short name	Rational and study objectives	Safety concern addressed	Study design	Study population	Milestones
ZOSTER-101: Long-term efficacy in adults 50 years of age and older. (Category 3)	To investigate long-term efficacy, safety and immunogenicity.	Long-term efficacy and assessment of the need for additional doses in adults 18 years of age and older. Long-term immunogenicity in adults 18 years of age and older.	Phase IIIb, open label, long-term follow-up of study ZOSTER-049 (follow-up of ZOSTER-006/022 studies)	Subjects 50 years of age or older from studies ZOSTER-006/022	Final study report: 23 Aug 2028
EPI-ZOSTER-030 VS US DB: Targeted safety study (TSS) to evaluate the safety of *Shingrix* in adults 50 years of age and older in the US. (Category 3)	To evaluate the safety of *Shingrix* in older adults (≥ 50 YOA) in the US.	Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination. Guillain-Barré syndrome (GBS)	Non-interventional (observational) cohort study	Adults 50 years of age or older in US	Final study report: 31 Mar 2027

Short name	Rational and study objectives	Safety concern addressed	Study design	Study population	Milestones
EPI-ZOSTER-032 VS US DB: Targeted safety study (TSS) to evaluate the safety of *Shingrix* in adults 65 years of age and older in the US. (Category 3)	To evaluate the safety of *Shingrix* in older adults (≥ 65 YOA) in the US Medicare population.	Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination.	Non-interventional (observational) cohort study US.	Adults 65 years of age or older in US	Final study report: 30 Jun 2027
EPI-ZOSTER-031: Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complication. (Category 3)	To estimate the effectiveness of *Shingrix* in preventing HZ, PHN and HZO in US subjects aged 50 years and above, overall and by age groups. To estimate long-term vaccine effectiveness up to 10 years after vaccination with *Shingrix*.	Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complication	An observational (non-interventional) retrospective cohort study	Subjects aged 50 years and above in the US	Final study report: 1 Aug 2033

III.3 Summary table of additional pharmacovigilance activities

Table 15 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
ZOSTER-101 Long-term efficacy in adults 50 years of age and older. Ongoing	To investigate long-term efficacy, safety and immunogenicity.	Long-term efficacy and assessment of the need for additional doses in adults 18 years of age and older. Long-term immunogenicity in adults 18 years of age and older.	Final report	23 Aug 2028

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
EPI-ZOSTER-030 VS US DB Targeted safety study (TSS) to evaluate the safety of *Shingrix* in adults 50 years of age and older in the U.S Ongoing	Non-interventional (observational) retrospective cohort study to evaluate the safety of *Shingrix* in older adults (≥ 50 YOA) in the US.	Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination. Guillain-Barré syndrome (GBS)	Final report	31 Mar 2027
EPI-ZOSTER-032 VS US DB Targeted safety study (TSS) to evaluate the safety of *Shingrix* in adults 65 years of age and older in the U.S Ongoing	Non-interventional (observational) targeted safety study to evaluate the safety of *Shingrix* in the Medicare population (65 YOA or older) in US	Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination.	Final report	30 Jun 2027
EPI-ZOSTER-031 Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complication Ongoing	To estimate the effectiveness of *Shingrix* in preventing HZ, PHN and HZO in US subjects aged 50 years and above, overall and by age groups.	Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complication	Final report	1 Aug 2033

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing imposed post-authorization efficacy studies.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table 16 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Guillain-Barré syndrome (GBS)	**Routine risk communication:** SmPC section 4.8
Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination (important potential risk)	None
Long-term efficacy and assessment of the need for additional doses in adults 18 years of age and older.	None
Long-term immunogenicity in adults 18 years of age and older	None
Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complications	None

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of *Shingrix*.

V.3 Summary of risk minimization measures

Table 17 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risk: Guillain-Barré syndrome (GBS)	**Routine risk minimization measures:** Wording in SmPC section 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires and other forms of routine pharmacovigilance activities for Guillain-Barré Syndrome **Additional pharmacovigilance activities**: EPI-ZOSTER-030 VS US DB

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important potential risk: Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination	No risk minimization measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: • Autoimmune thyroiditis • Gout • Idiopathic Thrombocytopenia • Inflammatory (non-infective) ocular disease • Inflammatory bowel disease • Leukocytoclastic vasculitis • Multiple Sclerosis • Optic ischemic neuropathy (arteritic and non-arteritic) • Optic neuritis • Polymyalgia rheumathica • Psoriasis • Rheumatoid arthritis • Still's disease (adult onset) • Temporal arteritis **Additional pharmacovigilance activities**: EPI-ZOSTER-030 VS US DB EPI-ZOSTER-032 VS US DB
Missing information: Long-term efficacy and assessment of the need for additional doses in adults 18 years of age and older.	No risk minimization measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** ZOSTER-101
Missing information: Long-term immunogenicity in adults 18 years of age and older.	No risk minimization measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** ZOSTER-101
Missing information: Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complications	No risk minimization measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** EPI-ZOSTER-031

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for *Shingrix*

This is a summary of the risk management plan (RMP) for *Shingrix*. The RMP details important risks of *Shingrix*, how these risks can be minimized, and how more information will be obtained about *Shingrix's* risks and uncertainties (missing information).

Shingrix's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how *Shingrix* should be used.

This summary of the RMP for *Shingrix* should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of *Shingrix's* RMP.

I. The medicine and what it is used for

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

- adults 50 years of age or older; and
- adults 18 years of age or older at increased risk of HZ (see SmPC for the full indication).

It contains the recombinant VZV gE antigen as active substance and the $AS01_B$ Adjuvant System and it is given by intramuscular injection.

Further information about the evaluation of *Shingrix*'s benefits can be found in *Shingrix*'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/*Shingrix*

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of *Shingrix*, together with measures to minimize such risks and the proposed studies for learning more about *Shingrix's* risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of *Shingrix* is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of *Shingrix* are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of *Shingrix*. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Guillain-Barré syndrome (GBS)
Important potential risks	• Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination
Missing information	• Long-term efficacy and assessment of the need for additional doses of the vaccine in adults of 18 years of age or above • Long-term immunogenicity in adults as of 18 years of age or above • Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complications

II.B Summary of important risks

Important identified risk: Guillain-Barré syndrome (GBS)	
Evidence for linking the risk to the medicine	GBS results from the PASS EPI-ZOSTER-032 VS US DB, to evaluate the safety of *Shingrix* in adults ≥65 years of age in the US, showed a statistically significant increased risk of GBS post any dose within the 42-day risk window (RR= 3.15 [95% CI: 1.82 - 5.68]). A summary of the study and the results have been provided below: **EPI-ZOSTER-032** The study EPI-ZOSTER-032 VS US DB is designed to address whether there is an increased risk of new-onset (incidence) GBS within 42 days (6 weeks) following at least 1 dose of *Shingrix* vaccination in US adults ≥65 years of age. Using the CMS Chronic Condition Warehouse Medicare database, the study employs self-controlled risk interval design, whereby each individual serves as their own control (Days 43-84). A total of 75 Medicare beneficiaries who met the inclusion criteria were included in the GBS analytic cohort. The mean age was 75.37 (±6.98) years, and 50.67% were females. Twenty-two received both doses of *Shingrix* while 53 received only 1 dose. Some of the commonly reported comorbidities included diabetes mellitus (16, 21.3%), chronic kidney disease (15, 20%), and chronic lung disease (12, 16%). The data were analyzed both descriptively which showed baseline demographic and health characteristics, and inferential analysis showed the risk of incident GBS in risk window relative to control using a conditional Poisson regression. The results showed 75 incident GBS cases post any dose, of which 57 (76%) cases were reported after Dose 1 and 18 after Dose 2. Of the 75 incident GBS cases, 57 were reported within the 42-day risk window while 18 were reported in Control window (43-84 days). The peak incidence is observed within 14 days post any dose in 25 (44%) cases and 32 cases occurred 15-42 days after exposure. The distribution of cases by *Shingrix* dose could not be displayed due to masking criteria (as per Medicare data use agreement, data cells <11 cannot be disclosed), even when aggregating the days. The primary analysis showed a statistically significant increased risk of GBS post any dose within the 42-day risk window (RR = 3.15 [95% CI: 1.82 - 5.68] and AR per million doses = 6.59 [95% CI: 4.35 – 7.96]). A similar trend was observed for secondary analysis when using the Fixed-3 week (RR =3.56 [95% CI: 1.69–8.65]; AR = 6.95 [95% CI: 3.94 – 8.54]) or 6-week Control window (RR = 3.17 [95% CI: 1.84–5.72]; AR = 6.61 [95% CI: 4.41 – 7.97]). Dose specific sensitivity analysis found an increased risk of GBS following Dose 1 (RR = 5.33 [95% CI: 2.59 – 12.36]; AR = 11.83 [95% CI: 8.94-13.38]) but not Dose 2. Seasonality adjusted and COVID-19 sensitivity analyses were also consistent with the primary analysis. Additional post-hoc analyses, such as excluding participants with baseline Gastrointestinal / Respiratory infection and those who received concomitant vaccinations (e.g., Influenza, Pneumococcal, Tdap) ≤42 days prior to *Shingrix* vaccination; PPV adjustment assuming 50% PPV age stratification showed consistent results though the risk was attenuated in adults aged 65-74 years as

	compared to the primary analysis. These results are consistent with the risk of GBS as observed in a study by Goud, 2021 (RR = 2.84 [95% CI: 1.53 – 5.27]; AR = 3.13 after extended study period).
Risk factors and risk groups	Incidence of GBS increases with age by 20% for every decade of age from 0.90 per 100 000 person-years in adults aged 20-29 years to 2.66 per 100 000 person-years in adults 80-89 years [Sejvar, 2011]. GBS is an immune-mediated polyneuropathy which can occur naturally in the adult population. Approximately two-thirds of GBS cases occur several days or weeks after an apparent infectious illness, commonly a gastrointestinal illness or upper respiratory tract infection. Campylobacter enteritis, influenza, cytomegalovirus, Epstein-Barr virus, HIV, chikungunya, Zika virus, and Mycoplasma pneumoniae have been implicated to be the trigger. Malignancies and surgical procedures also have been suggested to increase the risk of GBS [Chen, 2020].
Risk minimization measures	**Routine risk minimization measures:** Wording in SmPC section 4.8
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Short study name: EPI-ZOSTER-030 VS US DB See section II.C of this summary for an overview of the post- authorization development plan.

Important potential risk: Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination	
Evidence for linking the risk to the medicine	pIMDs are a subset of adverse events that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune aetiology. pIMDs are considered as a theoretical risk for all vaccines containing Adjuvant Systems (i.e. adjuvant combinations). In addition togenetic factors, environmental triggers (in particular, viruses, bacteria and other infectious pathogens) could play a major role in the development of pIMDs [Wraith, 2003]. This has stimulated the debate as to whether such diseases might also be triggered by vaccines, particularly based on their possible effects on the regulation of the immune system and the potential (yet theoretical) concern that they may induce unwanted immune processes in susceptible individuals. Case reports of autoimmune diseases temporally associated with the administration of vaccines (both adjuvanted and non-adjuvanted) have been described in the scientific literature. Most of these reports refer to vaccines targeting viral illnesses. Proposed mechanisms by which vaccines might induce autoimmune diseases are frequently extrapolated from the known capacity of the infectious agents that the vaccine targets [Tavares Da Silva, 2013].
Risk factors and risk groups	Naturally-occurring autoimmune diseases are multi-etiological conditions with multiple risk factors, including genetic predisposition. All ages are affected with onset from childhood to late adulthood, as well as all racial, ethnic and socioeconomic groups. No specific trend in terms of groups or risks factors has been identified in *Shingrix*.
Risk minimization	No risk minimization measures

measures	
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Short study name: EPI-ZOSTER-030 VS US DB, EPI-ZOSTER-032 VS US DB See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Long-term efficacy and assessment of the need for additional doses in adults 18 years of age and older	
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Short study name: ZOSTER-101 See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Long-term immunogenicity in adults 18 years of age and older	
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Short study name: ZOSTER-101 See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complications	
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance** **activities**: Short study name: EPI- ZOSTER-031 See section II.C of this summary for an overview of the post-authorization development plan.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of *Shingrix*.

II.C.2 Other studies in post-authorization development plan

Study short name	Purpose of the study
ZOSTER-101 Long-term efficacy in adults ≥50 years of age. (Category 3)	To investigate long-term efficacy, safety and immunogenicity.
EPI-ZOSTER-030 VS US DB Targeted safety study (TSS) to evaluate the safety of *Shingrix* in adults ≥50 years of age in the U.S (Category 3)	To evaluate the safety of *Shingrix* in older adults (≥50 YOA) in the US.
EPI-ZOSTER-032 VS US DB Targeted safety study (TSS) to evaluate the safety of *Shingrix* in adults ≥65 years of age in the U.S (Category 3)	To evaluate the safety of *Shingrix* in older adults (≥65 YOA) in the US.
EPI-ZOSTER-031 Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complication (Category 3)	To estimate the effectiveness of *Shingrix* in preventing HZ, PHN and HZO in US subjects aged 50 years and above, overall and by age groups. To estimate long-term vaccine effectiveness up to 10 years after vaccination with *Shingrix*.

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

The following targeted follow-up questionnaires are provided:

Targeted Follow-Up Questionnaire Shingrix and Autoimmune Thyroiditis (including Hashimoto Thyroiditis)

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to Autoimmune Thyroiditis in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***Try to fill this questionnaire as comprehensively as possible***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth:(dd/mm/yyyy) |____|____|_____|	Age: yy.mm |___ | ___|
Weight / Unit _____ / _____		Height / Unit _____ / _____	Gender: F ☐ M ☐

II. Description of the Event

1. Date of onset of symptoms (dd/mm/yyyy): |____|____|_____|

2. Clinical sign and or symptoms: *Please tick all that apply. For each sign and symptoms, please describe when possible:*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Ongoing Yes	Ongoing No	Stop date (dd/mm/yyyy)	Description
2.1	Goiter	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.2	Thickened, pale and dry skin, *specify*	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.3	Fatigue/Tiredness	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.4	Cold intolerance	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.5	Slow speech	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.6	Peripheral edema (non-pitting)	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.7	Edema of the face	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.8	Hair fragility	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.9	Bradycardia	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.10	Cardiomegaly	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.11	Constipation	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.12	Unexplained weight gain	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.13	Dyspnea	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.14	Hoarse voice	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.15	Memory impairment	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.16	Seizures	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.17	Menstrual disorders (oligomenorrhea, menomethrorragia)	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.18	Diminished deep tendon reflexes with prolonged relaxation phase	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
Other sign/symptoms? please specify		☐	☐	|___|___|____|	☐	☐	|___|___|____|	
3.0	Provide relevant results of physical examination:							
4.0	Prior to receiving the suspected SHINGRIX vaccine, were there similar signs or symptoms noticed? Yes ☐ No ☐ *If yes, please specify* _____							

III. Diagnostic Tests:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/ Titers	Reference Range
Free thyroxin (FT4)	|___|___|____|			
Thyroid stimulating hormone (TSH)	|___|___|____|			
Free triiodothyronine (FT3)	|___|___|____|			
anti-thyroperoxidase antibodies (anti-TPO)	|___|___|____|			
anti-thyroglobulin antibodies (anti-Tg)	|___|___|____|			
Thyroid Ultrasound	|___|___|____|			
Radioiodine thyroid uptake (RAIU)	|___|___|____|			
Radionuclide thyroid scan	|___|___|____|			
Fine needle aspiration (FNAB)	|___|___|____|			
Total cholesterol	|___|___|____|			
Triglycerides	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____|____|_____|	
☐ Resolved with Sequelae	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____|____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

V. Medical History

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases, *specifically:*				Disease is currently controlled?	
	Yes	No	Date of Diagnosis (dd/mm/yyyy)	Yes	No
• Hypoparathyroidism	☐	☐	|_____|_____|_____|	☐	☐
• POEMS syndrome (e.g. polyneuropathy, organomegaly, endocrinopathy ….)	☐	☐	|_____|_____|_____|	☐	☐
• Primary cortical adrenal insufficiency	☐	☐	|_____|_____|_____|	☐	☐
• Turner's syndrome	☐	☐	|_____|_____|_____|	☐	☐
• Addison's disease	☐	☐	|_____|_____|_____|	☐	☐

If yes, please specify diagnosis and describe the course of the illness:

6.2 Has the patient experienced previously other immune-mediated/autoimmune disease?	Yes ☐	No ☐

If yes, please specify diagnosis and describe the course of the illness:

6.3 Does the patient have a post medical history of any of the following: post radioactive iodine (I-131) therapy for hyperthyroidism, total or subtotal thyroidectomy, head/neck radiation therapy for malignancies, radiation injury, deiodinase enzyme deficiency?	Yes ☐	No ☐

If yes, please specify diagnosis and describe the course of the illness:

6.4 Does the patient have a family history of immune-mediated / autoimmune diseases?	Yes ☐	No ☐

If yes, please specify diagnosis and relationship to the patient (e.g. mother, father, brother…etc.):

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or route of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration	Administration route
SHINGRIX 1st			|_____|_____|_____|	
SHINGRIX 2nd			|_____|_____|_____|	
			|_____|_____|_____|	
			|_____|_____|_____|	

VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. For medications specified below, if the patient didn't take it, please leave it blank. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
Propylthiouracil			|___|___|____|/|___|___|____|	
Methimazole			|___|___|____|/|___|___|____|	
Carbimazole			|___|___|____|/|___|___|____|	
Lithium inhibits			|___|___|____|/|___|___|____|	
Amiodarone			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	

			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details

Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |_____|_____|_____|	Signature

Targeted Follow–Up Questionnaire
Shingrix and Gout

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to Giant cell arteritis or Temporal Arteritis in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***Try to fill this questionnaire as comprehensively as possible***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth: dd/mm/yyyy) |____|____|_____|	Age: (yy.mm) |____|____|
Weight/Unit _____/_____		Height / Unit _____/_____	Gender: F ☐ M ☐

II. Description of the Event:

1. **Date of onset symptoms (dd/mm/yyyy):** |_____|_____|_______|
2. **Clinical sign and symptoms:** *Please tick all that apply. For each sign and symptom, please specify where applicable:*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Is it still ongoing? Yes	No	Stop date (dd/mm/yyyy)	Description
2.1	Sudden, severe attacks of joint pain, redness, tenderness and swelling joints	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.2	Podagra (spontaneous onset of excruciating pain, edema, and inflammation in the metatarsal-phalangeal joint of the great toe)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.3	Acute arthritis in another location (*specify location and number of joints affected, symmetrical or asymmetrical*)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.4	Limited range of joint mobility	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.5	Tophi or inflammation in other synovial-based structures, such as bursae and tendons along the helix of the ear, fingers, toes, prepatellar bursa, olecranon, etc (*specify location and number of joints affected*)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
Other signs/symptoms? please specify:		☐	☐	|__|__|____|	☐	☐	|__|__|____|	

3.0	Provide relevant results of physical examination:	
4.0	Prior to receiving the suspected SHINGRIX vaccine, were there similar signs or symptoms noticed? Yes ☐	No ☐

If yes, please specify:

III. Diagnostic Tests:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/Titers	Reference Range
Complete blood count	|___|___|____|			
White blood cell (WBC)	|___|___|____|			
WBC differential	|___|___|____|			
Platelet count	|___|___|____|			
Erythrocyte Sedimentation Rate (ESR)	|___|___|____|			
Serum C-reactive protein (CRP)	|___|___|____|			
Serum urate (SU) concentration	|___|___|____|			
Synovial fluid analyses	|___|___|____|			
Total cholesterol	|___|___|____|			
Triglycerides	|___|___|____|			
X-ray of the affected joints	|___|___|____|			
Magnetic Resonance Image (MRI)	|___|___|____|			
Computerized tomography (CT) scan	|___|___|____|			
Musculoskeletal ultrasound	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____|____|_____|	
☐ Resolved with Sequelae	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____|____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

V. Medical History:

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases, *specifically*:				Disease is currently controlled?	
	Yes	No	Date of Diagnosis (dd/mm/yyyy)	Yes	No
• Obesity	☐	☐	|_____|_____|_____|	☐	☐
• Diabetes and metabolic syndrome	☐	☐	|_____|_____|_____|	☐	☐
• Renal disease	☐	☐	|_____|_____|_____|	☐	☐
• Cardiovascular disease	☐	☐	|_____|_____|_____|	☐	☐
• Untreated chronic hypertension	☐	☐	|_____|_____|_____|	☐	☐
• Organ transplantation	☐	☐	|_____|_____|_____|	☐	☐
• Recent surgery or trauma	☐	☐	|_____|_____|_____|	☐	☐

If yes, please describe the course of the illness:

6.2 Has the patient experienced previously other immune-mediated/autoimmune disease?	Yes ☐	No ☐
If yes, please specify diagnosis and describe the course of the illness:		
6.3 Has the patient experienced similar symptoms in the past?	Yes ☐	No ☐
If yes, please describe their pattern of progression:		
6.4 Does the patient have a current or past medical history of chronic hyperuricemia and/or hypertriglyceridemia?	Yes ☐	No ☐
If yes, please specify diagnosis and describe the course of the illness:		
6.5 Does the patient have a daily alcohol consumption of < 25 g/day (less than 2 drinks a day)?	Yes ☐	No ☐
6.6 Does the patient have a daily alcohol consumption of >60gr/day (>4 drinks a day)?	Yes ☐	No ☐
6.7 Does the patient take medications, including diuretics, low-dose aspirin, cyclosporine or levodopa?	Yes ☐	No ☐
If yes, please describe the course of the illness:		
6.8 Does the patient have a family history of immune-mediated / autoimmune diseases?	Yes ☐	No ☐
If yes, please specify the diagnosis and the relationship to the patient (e.g. mother, father, brother…etc.):		

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or route of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration (dd/mm/yyyy)	Administration route
SHINGRIX			|____|____|_____|	
SHINGRIX			|____|____|_____|	
			|____|____|_____|	
			|____|____|_____|	

VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
			|__|__|____|/|__|__|____|	
			|__|__|____|/|__|__|____|	

			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details

Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |_____|_____|_____|	Signature

`

Targeted Follow–Up Questionnaire
Shingrix and Guillain Barre Syndrome

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to Guillain Barre Syndrome in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***Try to fill this questionnaire as comprehensively as possible***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth: (dd/mm/yyyy) |_____|_____|_____|	Age: (yy.mm) |_____|_____|
Weight/Unit _____/_____		Height / Unit _____/_____	Gender: F ☐ M ☐

II. Description of the Event:

1. **Date of onset symptoms (dd/mm/yyyy):** \|_____\|_____\|_____\|
2. **Clinical sign and symptoms:** *Please tick all that apply. For each sign and symptom, please describe in detail when possible:*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Ongoing Yes	Ongoing No	Stop date (dd/mm/yyyy)	Description
2.1	Flaccid weakness	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.2	Paralysis of the limbs	☐	☐	|__|__|____|	☐	☐	|__|__|____|	☐ Bilateral ☐ Unilateral ☐ Symmetric ☐ Asymmetric
2.3	Ataxia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.4	Hyporeflexia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.5	Areflexia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.6	Ophthalmoplegia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.7	Paresthesia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.8	Facial muscle paralysis/ weakness	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.9	Neck muscle paralysis/weakness	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.10	Dysphasia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.11	Dysarthria	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.12	Respiratory failure	☐	☐	|__|__|____|	☐	☐	|__|__|____|	☐ Require endotracheal intubation ☐ Require mechanical ventilation
2.13	Decreased or absent deep tendon reflexes in weak limbs	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.14	Autonomic symptoms (specify)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
Other signs/symptoms? Please specify:		☐	☐	|__|__|____|	☐	☐	|__|__|____|	

3.0	Provide relevant results of physical neurological examination (*vital signs, deep tendon reflexes in affected limbs, motor function, cranial nerves and sensorium*)	
4.0	Prior to receiving the suspected SHINGRIX vaccine, were similar signs or symptoms noticed?	Yes ☐ No ☐
If yes, please specify:		

`

III. Diagnostic Tests:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/Titers	Reference Range
Complete blood count	|___|___|____|			
White blood cell (WBC)	|___|___|____|			
WBC differential	|___|___|____|			
Platelet count	|___|___|____|			
Erythrocyte Sedimentation Rate (ESR)	|___|___|____|			
Serum C-reactive protein (CRP)	|___|___|____|			
Cerebrospinal Fluid (CSF)				
• Protein level	|___|___|____|			
• WBC count	|___|___|____|			
• WBC differential	|___|___|____|			
• Red blood cell count	|___|___|____|			
• Glucose	|___|___|____|			
• Oligoclonal bands	|___|___|____|			
Anti-Ganglioside Antibodies (anti-GQ1b, anti-GD3, anti-GM1)	|___|___|____|			
Campylobacter jejuni testing (e.g. stool culture, serum IgA, IgG or IgM antibodies)	|___|___|____|			
Cytomegalovirus (CMV)	|___|___|____|			
Epstein-Barr Virus (EBV)	|___|___|____|			
Other relevant serology (specify)	|___|___|____|			
X-ray	|___|___|____|			
Electrocardiogram (ECG)	|___|___|____|			
Magnetic Resonance Image (MRI)	|___|___|____|			
Computerized tomography (CT) scan	|___|___|____|			
Nerve conduction studies	|___|___|____|			
Electromyography (EMG)	|___|___|____|			
Evoked potential studies	|___|___|____|			
Nerve biopsy	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____|____|_____|	
☐ Resolved with Sequelae	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____|____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

`

V. Medical History:

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases?

If yes, please describe the course of illness:

6.2 Has the patient previously experienced other immune-mediated/autoimmune disease?	Yes	☐	No	☐

If yes, please specify the diagnosis and describe the course of the illness:

6.3 Has the patient experienced similar symptoms in the past?	Yes	☐	No	☐

If yes, please describe the pattern of progression:

6.4 Does the patient have history of recent bacterial or viral infection?	Yes	☐	No	☐

If yes, please describe the course of the illness and specify the infectious agent :

6.5 Does the patient have a family history of immune-mediated / autoimmune diseases?	Yes	☐	No	☐

If yes, please specify the diagnosis and relationship to the patient (e.g. mother, father, brother…etc.):

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or route of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration	Administration route
SHINGRIX 1st			|_____|_____|________|	
SHINGRIX 2nd			|_____|_____|________|	
			|_____|_____|________|	
			|_____|_____|________|	

VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	

`

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details

Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |_____|_____|_____|	Signature

Targeted Follow–Up Questionnaire
Shingrix and Idiopathic Thrombocytopenia

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to Idiopathic or Immune-mediated Thrombocytopenia in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***Try to fill this questionnaire as comprehensively as possible***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth: (dd/mm/yyyy) |_____|_____|_____|	Age: (yy.mm) |_____|_____|
Weight/Unit _____/_____		Height / Unit _____/_____	Gender: F ☐ M ☐

II. Description of the Event:

1. **Date of onset symptoms (dd/mm/yyyy):** \|_____\|_____\|_____\|
2. **Clinical sign and symptoms:** *Please tick all that apply. For each sign and symptom, please describe in detail when possible:*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Ongoing Yes	Ongoing No	Stop date (dd/mm/yyyy)	Description
2.1	Petechiae, Purpura or ecchymoses (*specify easy or excessive bruising*)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.2	Epistaxis	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.3	Gingival bleeding	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.4	Bruising	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.5	Mucosal bleeding	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.6	Hemoptysis	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.7	Hematemesis	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.8	Hematuria	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.9	Hematochezia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.10	Melena	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.11	Menstrual disorders (menorrhagia, menometrorrhagia)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
Other signs/symptoms? please specify:		☐	☐	|__|__|____|	☐	☐	|__|__|____|	

3.0	Provide relevant results of physical examination		
4.0	Prior to receiving the suspected SHINGRIX vaccine, were there similar signs or symptoms noticed?	Yes ☐	No ☐

If yes, please specify:

`

III. Diagnostic Tests:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/Titers	Reference Range
Complete blood count	|___|___|____|			
White blood cell (WBC)	|___|___|____|			
WBC differential	|___|___|____|			
Platelet count	|___|___|____|			
Prothrombine time (PT)	|___|___|____|			
Activated partial tromboplastine time (aPTT)	|___|___|____|			
International Normalized Ratio (INR)	|___|___|____|			
Peripheral smear and morphologic examination	|___|___|____|			
Platelet-associated IgG	|___|___|____|			
Bone marrow aspiration	|___|___|____|			
Anti-platelet antibodies	|___|___|____|			
Antinuclear antibodies (ANA)	|___|___|____|			
Erythrocyte Sedimentation Rate (ESR)	|___|___|____|			
Serum C-reactive protein (CRP)	|___|___|____|			
Any other relevant/abnormal test results to rule out other causes of thrombocytopenia	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____|____|_____|	
☐ Resolved with Sequelae	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____|____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

`

V. Medical History:

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases, *specifically*:				Disease is currently controlled:	
	Yes	No	Date of Diagnosis (dd/mm/yyyy)	Yes	No
• HIV infection	☐	☐	|_____|_____|_____|	☐	☐
• Hepatitis C	☐	☐	|_____|_____|_____|	☐	☐
• Myelodysplastic syndrome	☐	☐	|_____|_____|_____|	☐	☐
• Systemic lupus erythematous	☐	☐	|_____|_____|_____|	☐	☐
• Organ dysfunction (liver failure, hepato- or splenomegaly)	☐	☐	|_____|_____|_____|	☐	☐
• Hematopoietic malignancy (lymphoma, leukemia)	☐	☐	|_____|_____|_____|	☐	☐

If yes, please describe the course of illness:

6.2 Has the patient experienced previously other immune-mediated/autoimmune disease? Yes ☐ No ☐

If yes, please specify diagnosis and describe the course of the illness:

6.3 Has the patient experienced similar symptoms in the past? Yes ☐ No ☐

If yes, please describe the pattern of progression:

6.4 Does the patient have a history of recent bacterial, viral, fungal infectious diseases other than listed above (*e.g. mumps, measles or respiratory infection …)?* Yes ☐ No ☐

If yes, please describe the course of the illness and infectious agent:

6.5 Does the patient have a family history of immune-mediated / autoimmune diseases? Yes ☐ No ☐

If yes, please specify the diagnosis and relationship to the patient (e.g. mother, father, brother, etc.):

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or route of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration	Administration route
SHINGRIX 1st			|____|____|_____|	
SHINGRIX 2nd			|____|____|_____|	
			|____|____|_____|	
			|____|____|_____|	

VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. For medications specified below, if the patient didn't take it, please leave it blank. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
Cytotoxic drugs			|___|___|____|/|___|___|____|	
Thiazide diuretics			|___|___|____|/|___|___|____|	
Interferon			|___|___|____|/|___|___|____|	
Gold salts			|___|___|____|/|___|___|____|	
Heparin			|___|___|____|/|___|___|____|	
Aspirin			|___|___|____|/|___|___|____|	
Nonsteroidal anti-inflammatory agents (NSAID)			|___|___|____|/|___|___|____|	

`			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details

Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |_____|_____|_____|	Signature

`

Targeted Follow–Up Questionnaire Shingrix and Optic inflammatory (non-infective) conditions

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to inflammatory (non-infective) ocular disease in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***Try to fill this questionnaire as comprehensively as possible***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth: (dd/mm/yyyy) |_____|_____|_____|	Age: (yy.mm) |_____|_____|
Weight/Unit _____/_____		Height / Unit _____/_____	Gender: F ☐ M ☐

II. Description of the Event:

1. **Date of onset symptoms (dd/mm/yyyy):** |_____|_____|_____|
2. **Clinical sign and symptoms:** *Please tick all that apply. For each sign and symptom, please describe in detail when possible:*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Ongoing Yes	Ongoing No	Stop date (dd/mm/yyyy)	Description
2.1	Eye pain	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.2	Eye redness	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.3	Floaters	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.4	Decreased/blurred vision	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.5	Vision loss (*specify transient or permanent*)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.6	Photophobia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.7	Mass lesions	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.8	Epiphora (tearing)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.9	Diplopia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
Other signs/symptoms? Please specify:		☐	☐	|__|__|____|	☐	☐	|__|__|____|	

3.0	Provide relevant results of physical and ophthalmological examinations:		
4.0	Prior to receiving the suspected SHINGRIX vaccine, were similar signs or symptoms noticed?	Yes ☐	No ☐

If yes, please specify:

`

III. Diagnostic Tests:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/Titers	Reference Range
Complete blood count	|___|___|____|			
White blood cell (WBC)	|___|___|____|			
WBC differential	|___|___|____|			
Platelet count	|___|___|____|			
Erythrocyte Sedimentation Rate (ESR)	|___|___|____|			
Serum C-reactive protein (CRP)	|___|___|____|			
Rheumatoid Factor (RF)	|___|___|____|			
Serum-angiotensin converting enzyme (ACE)	|___|___|____|			
c-ANCA autoantibody	|___|___|____|			
p-ANCA autoantibody	|___|___|____|			
anti-thyroid antibodies				
• anti-thyroperoxidase antibodies (anti-TPO)	|___|___|____|			
• anti-thyroglobulin antibodies (anti-Tg)	|___|___|____|			
Thyroid function studies	|___|___|____|			
• Free thyroxin (FT4)	|___|___|____|			
• Thyroid stimulating hormone (TSH)	|___|___|____|			
• Free triiodothyronine (FT3)	|___|___|____|			
Serum protein electrophoresis	|___|___|____|			
Magnetic Resonance Image (MRI)	|___|___|____|			
Computerized tomography (CT) scan	|___|___|____|			
Chest X-ray	|___|___|____|			
Orbital Ultrasonography	|___|___|____|			
Biopsy	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____|____|_____|	
☐ Resolved with Sequelae,	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____|____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

V. Medical History:

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases, *specifically:*	Yes	No	Date of Diagnosis (dd/mm/yyyy)	Disease is currently controlled: Yes	No
• Rheumatoid arthritis	☐	☐	|_____|_____|_____|	☐	☐
• Systemic lupus erythematosus	☐	☐	|_____|_____|_____|	☐	☐
• Sarcoidosis	☐	☐	|_____|_____|_____|	☐	☐
• Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	☐	☐	|_____|_____|_____|	☐	☐
• Polyarteritis nodosa	☐	☐	|_____|_____|_____|	☐	☐
• Relapsing polychondritis	☐	☐	|_____|_____|_____|	☐	☐
• Wegener's granulomatosis	☐	☐	|_____|_____|_____|	☐	☐
• Scleroderma	☐	☐	|_____|_____|_____|	☐	☐

If yes, please describe the course of illness:

6.2 Has the patient previously experienced other immune-mediated/autoimmune disease? Yes ☐ No ☐

If yes, please specify diagnosis and describe the course of the illness:

6.3 Does the patient have a history of ocular allergy? Yes ☐ No ☐

If yes, please specify?

6.4 Has the patient had other ocular diseases in the past? (e.g. Birdshot retinochoroidopathy, Fuchs'heterochromic iridocyclitis, Vogt-Koyanagi-Harada, and ocular cicatricial pemphigoid….) Yes ☐ No ☐

If yes, please specify diagnosis and describe the course of the illness:

6.5 Does the patient have a history of a recent bacterial, viral, fungal, or parasite infection? Yes ☐ No ☐

If yes, please describe the course of the illness and infectious agent:

6.6 Does the patient have a recent history of conjunctivitis, scleritis, keratitis, uveitis, retinal vasculitis, optic neuropathy, dacryoadenitis? Yes ☐ No ☐

If yes, please specify diagnosis and describe the course of the illness:

6.7 Does the patient have a family history of immune-mediated / autoimmune diseases? Yes ☐ No ☐

If yes, please specify the diagnosis and relationship to the patient (e.g. mother, father, brother…etc.):

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or route of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration	Administration route
SHINGRIX 1st			|____|____|_____|	
SHINGRIX 2nd			|____|____|_____|	
			|____|____|_____|	
			|____|____|_____|	

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VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. For medications specified below, if the patient didn't take it, please leave it blank. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
Rifabutin			|___|___|____|/|___|___|____|	
Fluoroquinolones			|___|___|____|/|___|___|____|	
Bisphosphonates			|___|___|____|/|___|___|____|	
Sulfonamides			|___|___|____|/|___|___|____|	
Diethylcarbamazine			|___|___|____|/|___|___|____|	
Anti-TNF drugs			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details

Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |_____|_____|_____|	Signature

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

Targeted Follow – Up Questionnaire Shingrix and Inflammatory Bowel Diseases (Crohn's disease and Ulcerative Colitis)

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to Inflammatory Bowel Diseases in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***Try to fill this questionnaire as comprehensively as possible***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth: (dd/mm/yyyy) |_____|_____|_____|	Age: (yy.mm) |_____|_____|
Weight/Unit _____/_____		Height / Unit _____/_____	Gender: F ☐ M ☐

II. Description of the Event:

1. **Date of onset symptoms (dd/mm/yyyy):** |_____|_____|_____|
2. **Clinical sign and symptoms:** *Please tick all that apply. For each sign and symptom, please describe in detail when possible:*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Ongoing Yes	Ongoing No	Stop date (dd/mm/yyyy)	Description
2.1	Diarrhea (*specify bloody or not?)*	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.2	Fever	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.3	Abdominal pain and cramping	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.4	Rectal tenesmus	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.5	Fecal urgency/incontinence	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.6	Intestinal obstruction	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.7	Abdominal mass	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.8	Hematochezia or Rectal bleeding	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.9	Dysphagia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.10	Perianal disease (*e.g. fistulae, abscess, and fissure….please specify*)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.11	Vomiting	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.12	Unintended weight loss	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.13	Fatigue	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.14	Anorexia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.15	Ocular disorders(uveitis, episcleritis)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.16	Skin disorders	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.17	Peripheral arthritis (*specify location, symmetric or asymmetric?)*	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.18	Enthesitis	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.19	Sacroiliitis	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.20	Malnutrition	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
Other signs/symptoms? please specify:		☐	☐	|__|__|____|	☐	☐	|__|__|____|	

3.0	Provide relevant results of physical examination:		
4.0	Prior to receiving the suspected SHINGRIX vaccine, were there similar signs or symptoms noticed?	Yes ☐	No ☐
If yes, please specify:			

III. Diagnostic texts:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/Titers	Reference Range
Complete blood count	|___|___|____|			
White blood cell (WBC)	|___|___|____|			
WBC differential	|___|___|____|			
Platelet count	|___|___|____|			
Erythrocyte Sedimentation Rate (ESR)	|___|___|____|			
Serum C-reactive protein (CRP)	|___|___|____|			
Serum Albumin	|___|___|____|			
Serum Iron	|___|___|____|			
liver function tests				
• alanine transaminase (ALT)	|___|___|____|			
• aspartate transaminase (AST)	|___|___|____|			
• alkaline phosphatase (ALP)	|___|___|____|			
• gamma-glutamyl transpeptidase (GGT)	|___|___|____|			
• total Bilirubin	|___|___|____|			
Stool tests				
• Blood	|___|___|____|			
• Leucocytes	|___|___|____|			
• Enteric pathogens (*e.g. Salmonella, Shigella, Yersinia, Campylobacter, E coli, Clostridium difficile…)*	|___|___|____|			
• Fecal calprotectin	|___|___|____|			
Anti-neutrophil cytoplasmic antibodies (ANCAs: pANCA, xANCA or atypical ANCA)	|___|___|____|			
Anti-saccharomyces cerevisiae antibodies (ASCA)	|___|___|____|			
Anti-intestinal goblet cell autoantibodies (GABs)	|___|___|____|			
Endoscopy sigmoidoscopy	|___|___|____|			
Colonoscopy	|___|___|____|			
Biopsy	|___|___|____|			
Magnetic Resonance Image (MRI)	|___|___|____|			
Computerized tomography (CT) scan	|___|___|____|			
Abdominal X-ray	|___|___|____|			
Abdominal Barium enema contrast studies	|___|___|____|			
Ultrasonography	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____|____|_____|	
☐ Resolved with Sequelae,	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____||____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

v. Medical History:

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases, *specifically:*				Disease is currently controlled?	
	Yes	No	Date of Diagnosis (dd/mm/yyyy)	Yes	No
• Autoimmune Hepatitis	☐	☐	|_____|_____|_____|	☐	☐
• Erythema nodosum	☐	☐	|_____|_____|_____|	☐	☐
• Primary Sclerosing Cholangitis	☐	☐	|_____|_____|_____|	☐	☐
• Pyoderma Gangrenosum	☐	☐	|_____|_____|_____|	☐	☐
• Ankylosing Spondylitis	☐	☐	|_____|_____|_____|	☐	☐
• Uveitis	☐	☐	|_____|_____|_____|	☐	☐
• Thromboembolic diseases	☐	☐	|_____|_____|_____|	☐	☐
• Urolithiasis	☐	☐	|_____|_____|_____|	☐	☐
If yes, please describe the diagnosis and course of the illness:					
6.2 Has the patient experienced previously other immune-mediated/autoimmune disease?				Yes ☐	No ☐
If yes, please specify diagnosis and describe the course of the illness:					
6.3 Has the patient had similar symptoms in the past?				Yes ☐	No ☐
If yes, please describe their pattern of progression:					
6.4 Does the patient have a significant smoking history? *If yes, for how many years?*				Yes ☐	No ☐
6.5 Does the patient have a medical history of a recent bacterial infection? (*e.g. Campylobacter jejuni)*				Yes ☐	No ☐
If yes, please specify diagnosis and describe the course of the illness:					
6.6 Does the patient have a family history of immune-mediated / autoimmune diseases?				Yes ☐	No ☐
If yes, please specify the diagnosis and relationship to the patient (e.g. mother, father, brother…etc.):					

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or route of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration	Administration route
SHINGRIX			|_____|_____|_____|	
SHINGRIX			|_____|_____|_____|	
			|_____|_____|_____|	
			|_____|_____|_____|	

VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. For medications specified below, if the patient didn't take it, please leave it blank. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
NSAIDs			|___|___|____|/|___|___|____|	
Isotretinoin			|___|___|____|/|___|___|____|	
Ibuprofen			|___|___|____|/|___|___|____|	

` Naproxen sodium			|___|___|____|/|___|___|____|	
Diclofenac sodium			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details

Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |_____|_____|_____|	Signature

Targeted Follow–Up Questionnaire
Shingrix and Leukocytoclastic Vasculitis

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to Leukocytoclastic Vasculitis in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***Try to fill this questionnaire as comprehensively as possible***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth: (dd/mm/yyyy) |_____|_____|_____|	Age: (yy.mm) |_____|_____|
Weight/Unit _____/_____		Height / Unit _____/_____	Gender: F ☐ M ☐

II. Description of the Event:

1. **Date of onset symptoms (dd/mm/yyyy):** \|_____\|_____\|_____\|
2. **Clinical sign and symptoms:** *Please tick all that apply. For each sign and symptom, please describe in detail when possible:*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Ongoing Yes	Ongoing No	Stop date (dd/mm/yyyy)	Description
2.1	Burning, pruritus or pain	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.2	Palpable purpura (*specify size of individual lesion, extent, location*)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.3	Erythematous macules	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.4	Urticarial lesions	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.5	Livedo reticularis	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.6	Nodules	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.7	Ulcerations	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.8	Fever	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.9	Abdominal pain	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.10	Vomiting	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.11	Arthralgia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.12	Myalgia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.13	Weight loss	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
Other signs/symptoms? please specify:		☐	☐	|__|__|____|	☐	☐	|__|__|____|	

3.0	Provide relevant results of physical examinations		
4.0	Prior to receiving the suspected SHINGRIX vaccine, were there similar signs or symptoms noticed?	Yes ☐	No ☐

If yes, please specify:

`

III. Diagnostic Tests:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/Titers	Reference Range
Complete blood count	|___|___|____|			
White blood cell (WBC)	|___|___|____|			
WBC differential	|___|___|____|			
Platelet count	|___|___|____|			
Erythrocyte Sedimentation Rate (ESR)	|___|___|____|			
Serum C-reactive protein (CRP)	|___|___|____|			
Serum creatinine	|___|___|____|			
Urea nitrogen	|___|___|____|			
Electrolytes	|___|___|____|			
Liver enzymes				
• alanine transaminase (ALT)	|___|___|____|			
• aspartate transaminase (AST)	|___|___|____|			
• alkaline phosphatase (ALP)	|___|___|____|			
• gamma-glutamyl transpeptidase (GGT)	|___|___|____|			
• total Bilirubin	|___|___|____|			
Urine analysis (protein and cellular casts)	|___|___|____|			
Hepatitis B and C viral markers	|___|___|____|			
• HBsAg	|___|___|____|			
• Anti-HCV	|___|___|____|			
• HCV RNA	|___|___|____|			
• ASO titers	|___|___|____|			
Rheumatoid Factor (RF)	|___|___|____|			
Tissue biopsy (skin, muscle, nerve)	|___|___|____|			
Complement levels (C3, C4, CH50)	|___|___|____|			
Cryoglobulins	|___|___|____|			
Anti-neutrophil cytoplasmic antibodies (ANCAs)	|___|___|____|			
Anti-nuclear antibody (ANA	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____|____|_____|	
☐ Resolved with Sequelae	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____|____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

V. Medical History:

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases, *specifically:*	Yes	No	Date of Diagnosis (dd/mm/yyyy)	Disease is currently controlled: Yes	No
• Hepatitis C infection	☐	☐	|_____|_____|_____|	☐	☐
• Hepatitis infection	☐	☐	|_____|_____|_____|	☐	☐
• HIV infection	☐	☐	|_____|_____|_____|	☐	☐
• Malignancy	☐	☐	|_____|_____|_____|	☐	☐
• Inflammatory Bowel Disease	☐	☐	|_____|_____|_____|	☐	☐
• Systemic lupus erythematosus	☐	☐	|_____|_____|_____|	☐	☐
• Rheumatoid arthritis	☐	☐	|_____|_____|_____|	☐	☐

If yes, please describe the course of illness:

6.2 Has the patient experienced previously other immune-mediated/autoimmune disease? Yes ☐ No ☐

If yes, please specify diagnosis and describe the course of the illness:

6.3 Does the patient have a history of: Yes ☐ No ☐

6.3.1 Recent infection (*e.g. upper respiratory tract infections in particular with beta-hemolytic streptococcus, gastroenteritis, bacterial endocarditis*)? Yes ☐ No ☐

6.3.2 Tick bites Yes ☐ No ☐

6.3.3 Others, *please specify* Yes ☐ No ☐

If yes, please specify diagnosis and describe the course of the illness

6.4 Has the patient experienced similar symptoms in the past? Yes ☐ No ☐

If yes, please describe the pattern of progression:

6.5 Does the patient have a family history of immune-mediated / autoimmune diseases? Yes ☐ No ☐

If yes, please specify the diagnosis and relationship to the patient (e.g. mother, father, brother…. etc.):

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or route of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration	Administration route
SHINGRIX 1st			|____|____|_____|	
SHINGRIX 2nd			|____|____|_____|	
			|____|____|_____|	
			|____|____|_____|	

VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. For medications specified below, if the patient didn't take it, please leave it blank. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
NSAIDs			|___|___|____|/|___|___|____|	
Penicillin's			|___|___|____|/|___|___|____|	
Anti-thyroid agents			|___|___|____|/|___|___|____|	
Quinolones			|___|___|____|/|___|___|____|	

Anti-TNF agents			|___|___|____|/|___|___|____|	
Leukotriene inhibitors			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details

Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |_____|_____|_____|	Signature

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Targeted Follow–Up Questionnaire
Shingrix and Multiple Sclerosis

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to Multiple Sclerosis in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***Try to fill this questionnaire as comprehensively as possible***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth: (dd/mm/yyyy) |_____|_____|_____|	Age: (yy.mm) |_____|_____|
Weight/Unit _____/_____		Height / Unit _____/_____	Gender: F ☐ M ☐

II. Description of the Event:

1. **Date of onset symptoms (dd/mm/yyyy):** |_____|_____|_____|
2. **Clinical sign and symptoms:** *Please tick all that apply. For each sign and symptom, please describe in detail when possible:*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Ongoing Yes	Ongoing No	Stop date (dd/mm/yyyy)	Description
2.1	Blurred vision	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.2	Double vision	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.3	Cognitive disorder	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.4	Paralysis/paresis in one or more limbs (*specify which limb, bilateral…*)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.5	Lack of coordination or ataxia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.6	Dizziness	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.7	Vertigo	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.8	Altered balance and gait	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.9	Paresthesias	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.10	Dysesthesias	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.11	Weakness or fatigue	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.12	Muscle pain and spasms	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.13	Bladder dysfunction	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.14	Bowel dysfunction	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.15	Sexual dysfunction	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.16	Hearing loss	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.17	Visual disturbances (nystagmus, optic neuritis, phosphenes, diplopia)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
Other signs/symptoms? please specify:		☐	☐	|__|__|____|	☐	☐	|__|__|____|	

3.0	Provide relevant results of neurological examination (*vital signs, deep tendon reflexes in affected limbs, motor function, cranial nerves and sensorium*)
4.0	Prior to receiving the suspected SHINGRIX vaccine, were there similar signs or symptoms noticed? Yes ☐ No ☐
If yes, please specify:	

`

III. Diagnostic Tests:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/Titers	Reference Range
Complete blood count	|___|___|____|			
White blood cell (WBC)	|___|___|____|			
WBC differential	|___|___|____|			
Platelet count	|___|___|____|			
Erythrocyte Sedimentation Rate (ESR)	|___|___|____|			
Serum C-reactive protein (CRP)	|___|___|____|			
Viral serology (specify)	|___|___|____|			
Magnetic Resonance Image (MRI) of Brain and/or spinal cord: specify level and number of lesions	|___|___|____|			
Cerebrospinal Fluid (CSF)				
• Protein level	|___|___|____|			
• WBC count	|___|___|____|			
• WBC differential	|___|___|____|			
• Red blood cell count	|___|___|____|			
• Glucose	|___|___|____|			
• Oligoclonal bands	|___|___|____|			
Nerve conduction studies	|___|___|____|			
Electromyography (EMG)	|___|___|____|			
Evoked potential studies	|___|___|____|			
Biopsy	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____|____|_____|	
☐ Resolved with Sequelae	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____|____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

`

V. Medical History:

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases, *specifically*:

	Yes	No	Date of Diagnosis (dd/mm/yyyy)	Disease is currently controlled: Yes	No
• Epstein-Barr virus (EBV) infection	☐	☐	|____|____|______|	☐	☐
• Human herpes virus 6 (HHV-6) infection	☐	☐	|____|____|______|	☐	☐
• Type I diabetes	☐	☐	|____|____|______|	☐	☐
• Inflammatory bowel disease	☐	☐	|____|____|______|	☐	☐
• Optic neuritis	☐	☐	|____|____|______|	☐	☐
• Graves' disease	☐	☐	|____|____|______|	☐	☐

If yes, please describe the course of illness:

6.2 Has the patient experienced previously other immune-mediated/autoimmune disease? Yes ☐ No ☐

If yes, please specify diagnosis and describe the course of the illness:

6.3 Has the patient experienced similar symptoms in the past? Yes ☐ No ☐

If yes, please describe the pattern of progression:

6.4 Is the patient a current smoker? *If yes, for how many years?* Yes ☐ No ☐

6.5 Does the patient have a family history of immune-mediated / autoimmune diseases? Yes ☐ No ☐

If yes, please specify diagnosis and relationship to the patient (e.g. mother, father, brother…etc.):

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or route of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration	Administration route
SHINGRIX 1st			|____|____|______|	
SHINGRIX 2nd			|____|____|______|	
			|____|____|______|	
			|____|____|______|	

VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	

`

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details

Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |_____|_____|_____|	Signature

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

Targeted Follow – Up Questionnaire Shingrix and Optic Ischemic Neuropathy (Arteritic and Non-Arteritic)

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to optic ischemic neuropathy in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***Try to fill this questionnaire as comprehensively as possible***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth: (dd/mm/yyyy) |_____|_____|_____|	Age: (yy.mm) |_____|_____|
Weight/Unit _____/_____		Height / Unit _____/_____	Gender: F ☐ M ☐

II. Description of the Event:

1. **Date of onset symptoms (dd/mm/yyyy):** \|_____\|_____\|_____\|
2. **Clinical sign and symptoms:** *Please tick all that apply. For each sign and symptom, please describe in detail when possible:*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Ongoing Yes	Ongoing No	Stop date (dd/mm/yyyy)	Description
2.1	Vision loss (*describe if transient or permanent, sudden or insidious*)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.2	Isolated, painless, sudden vision loss in one eye	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.3	Minimal to no cup-to-disc ratio ('disc at risk')	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.4	Chalk white, diffuse edema of the optic disc	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.5	Visual field defect	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.6	Amaurosis Fugax	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.7	Painful jaw muscle spasms or claudication	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.8	Unintentional weight loss	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.9	Fever	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.10	Localized headache	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
Other signs/symptoms? please specify:		☐	☐	|__|__|____|	☐	☐	|__|__|____|	

3.0	Provide relevant results of physical examination including visual acuity, ophthalmoscope and visual field testing:		
4.0	Prior to receiving the suspected SHINGRIX vaccine, were there similar signs or symptoms noticed?	Yes ☐	No ☐

If yes, please specify:

`

III. Diagnostic Tests:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/Titers	Reference Range
Complete blood count	|___|___|____|			
White blood cell (WBC)	|___|___|____|			
WBC differential	|___|___|____|			
Hematocrit	|___|___|____|			
Erythrocyte Sedimentation Rate (ESR)	|___|___|____|			
Serum C-reactive protein (CRP)	|___|___|____|			
Temporal Artery biopsy	|___|___|____|			
Fluorescein fundus angiography	|___|___|____|			
Magnetic Resonance Image (MRI)	|___|___|____|			
Computerized tomography (CT) scan	|___|___|____|			
Optical coherence tomography (OCT)	|___|___|____|			
Optic cup/disc ratio	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____|____|_____|	
☐ Resolved with Sequelae	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____|____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

`

V. Medical History:

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases, *specifically*:	Yes	No	Date of Diagnosis (dd/mm/yyyy)	Disease is currently controlled: Yes	No
• Giant cell arteritis (temporal arteritis)	☐	☐	|______|______|________|	☐	☐
• Hypertension	☐	☐	|______|______|________|	☐	☐
• Ischemic heart disease	☐	☐	|______|______|________|	☐	☐
• Hyperlipidemia	☐	☐	|______|______|________|	☐	☐
• Hypercholesterolemia	☐	☐	|______|______|________|	☐	☐
• Diabetes mellitus	☐	☐	|______|______|________|	☐	☐
• Market optic disc edema due to any cause	☐	☐	|______|______|________|	☐	☐
• Nocturnal arterial hypotension	☐	☐	|______|______|________|	☐	☐

If yes, please describe the course of illness:

6.2 Has the patient previously experienced other immune-mediated/autoimmune disease? Yes ☐ No ☐

If yes, please specify diagnosis and describe the course of the illness:

6.3 Has the patient had any previously eye operations (including laser surgery) Yes ☐ No ☐

If yes, please describe the course of the illness:

6.4 Does the patient have a history of a recent bacterial, viral, fungal, or parasite infection? Yes ☐ No ☐

If yes, please describe the course of the illness and infectious agent :

6.5 Does the patient have a recent history of conjunctivitis, scleritis, keratitis, uveitis, retinal vasculitis, optic neuropathy, dacryoadenitis? Yes ☐ No ☐

If yes, please specify diagnosis and describe the course of the illness:

6.6 Does the patient have a family history of immune-mediated / autoimmune diseases? Yes ☐ No ☐

If yes, please specify the diagnosis and relationship to the patient (e.g. mother, father, brother…etc.):

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or route of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration	Administration route
SHINGRIX 1st			|_____|_____|________|	
SHINGRIX 2nd			|_____|_____|________|	
			|_____|_____|________|	
			|_____|_____|________|	

VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	

`			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details

Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |_____|_____|_____|	Signature

Targeted Follow–Up Questionnaire
Shingrix and Optic Neuritis

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to Optic Neuritis in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***Try to fill this questionnaire as comprehensively as possible***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth: (dd/mm/yyyy) |_____|_____|_____|	Age: (yy.mm) |_____|_____|
Weight/Unit _____/_____		Height / Unit _____/_____	Gender: F ☐ M ☐

II. Description of the Event:

1. **Date of onset symptoms (dd/mm/yyyy):** |_____|_____|_____|
2. **Clinical sign and symptoms:** *Please tick all that apply. For each sign and symptom, please describe in detail when possible:*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Ongoing Yes	Ongoing No	Stop date (dd/mm/yyyy)	Description
2.1	Eye pain on movement	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.2	Visual changes (*specify unilateral or bilateral?*)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.3	Visual loss (*specify partial or complete?)*	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.4	Diplopia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.5	Change in color vision	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.6	Flashing lights	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
Other signs/symptoms? please specify:		☐	☐	|__|__|____|	☐	☐	|__|__|____|	

3.0	Provide relevant results of neurological and ophthalmological examinations		
4.0	Prior to receiving the suspected SHINGRIX vaccine, were there similar signs or symptoms noticed?	Yes ☐	No ☐

If yes, please specify:

`

III. Diagnostic Tests:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/Titers	Reference Range
Complete blood count	|___|___|____|			
White blood cell (WBC)	|___|___|____|			
WBC differential	|___|___|____|			
Platelet count	|___|___|____|			
Electrolytes	|___|___|____|			
Erythrocyte Sedimentation Rate (ESR)	|___|___|____|			
Serum C-reactive protein (CRP)	|___|___|____|			
Lyme serology	|___|___|____|			
Blood glucose	|___|___|____|			
Viral serology (specify)	|___|___|____|			
Cerebrospinal Fluid analysis (CSF)	|___|___|____|			
• CSF protein level	|___|___|____|			
• CSF white blood cell count	|___|___|____|			
• CSF differential	|___|___|____|			
• CSF red blood cell count	|___|___|____|			
• CSF glucose	|___|___|____|			
• Oligoclonal bands	|___|___|____|			
Nerve conduction studies	|___|___|____|			
Fluorescein angiography	|___|___|____|			
Visual evoked response study	|___|___|____|			
Optic coherence tomography (OCT)	|___|___|____|			
Magnetic Resonance Image (MRI)	|___|___|____|			
Computerized tomography (CT) scan	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____|____|_____|	
☐ Resolved with Sequelae	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____|____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

V. Medical History:

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases, *specifically*:

	Yes	No	Date of Diagnosis (dd/mm/yyyy)	Disease is currently controlled: Yes	No
• Demyelinating diseases (e.g. multiple sclerosis)	☐	☐	|____|____|______|	☐	☐
• Neuromyelitis optica (Devic's syndrome)	☐	☐	|____|____|______|	☐	☐
• Sarcoidosis	☐	☐	|____|____|______|	☐	☐
• Guillain-Barre syndrome	☐	☐	|____|____|______|	☐	☐
• Systemic lupus erythematosus	☐	☐	|____|____|______|	☐	☐
• Cranial tumors (e.g. meningioma)	☐	☐	|____|____|______|	☐	☐
• Head trauma	☐	☐	|____|____|______|	☐	☐

If yes, please describe the course of illness:

6.2 Has the patient previously experienced other immune-mediated/autoimmune disease? Yes ☐ No ☐

If yes, please describe the diagnosis and course of the illness:

6.3 Has the patient lived in a region where Lyme disease is endemic? Yes ☐ No ☐

If yes, is there a history of tick bite? Yes ☐ No ☐

Or history of rash consistent with erythema migrans? Yes ☐ No ☐

If yes, please describe the course of the illness

6.4 Has the patient recently treated with steroid medications, quinine and antibiotics? Yes ☐ No ☐

If yes, please specify

6.5 Does the patient have history of recent infections (e.g. mumps, measles, tuberculosis, viral encephalitis, sinusitis, meningitis, shingles, etc?) Yes ☐ No ☐

If yes, please specify:

6.6 Has the patient lived at a high latitude? *If yes, how many years?* Yes ☐ No ☐

6.7 Does the patient have a family history of immune-mediated / autoimmune diseases? Yes ☐ No ☐

If yes, please specify the diagnosis and relationship to the patient (e.g. mother, father, brother…etc.):

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or route of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration	Administration route
SHINGRIX 1st			|____|____|______|	
SHINGRIX 2nd			|____|____|______|	
			|____|____|______|	

VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	

`			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details

Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |_____|_____|_____|	Signature

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

Targeted Follow–Up Questionnaire
Shingrix and Polymyalgia Rheumatica

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to polymyalgia rheumatic disease in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge.***
- ***Try to fill this questionnaire as comprehensively as possible.***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth: (dd/mm/yyyy) |_____|_____|_____|	Age: (yy.mm) |_____|_____|
Weight/Unit _____/_____		Height / Unit _____/_____	Gender: F ☐ M ☐

II. Description of the Event:

1. **Date of onset symptoms (dd/mm/yyyy):** \|_____\|_____\|_____\|
2. **Clinical sign and symptoms:** *Please tick all that apply. For each sign and symptom, please describe in detail when possible.*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Ongoing Yes	Ongoing No	Stop date (dd/mm/yyyy)	Description
2.1	Muscle pain and stiffness in neck and/or shoulder (*please specify)*	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.2	Muscle pain and stiffness in arms and/or hips *(please specify)*	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.3	The above symptoms worsening in the morning due to prolonged inactivity	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.4	Bilateral upper arm tenderness or motion limitation	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.5	Fatigue	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.6	Malaise	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.7	Anorexia	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.8	Arthritis of the hands	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.9	Arthralgia of the hands	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.10	Pitting edema of the hands	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.11	Unexplained weight loss	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.12	Anemia	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
2.13	Depression	☐	☐	|___|___|____|	☐	☐	|___|___|____|	
Other signs/symptoms? please specify:		☐	☐	|___|___|____|	☐	☐	|___|___|____|	

3.0	Provide relevant results of physical examination:	
4.0	Prior to receiving the suspected SHINGRIX vaccine, were there similar signs or symptoms noticed?	Yes ☐ No ☐

If yes, please specify:

III. Diagnostic Tests:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/Titers	Reference Range
Complete blood count	|___|___|____|			
White blood cell (WBC)	|___|___|____|			
WBC differential	|___|___|____|			
Platelet count	|___|___|____|			
Erythrocyte Sedimentation Rate (ESR)	|___|___|____|			
Serum C-reactive protein (CRP)	|___|___|____|			
Rheumatoid Factor (RF)	|___|___|____|			
Anti-cyclic citrullinated peptides (anti-CCP)	|___|___|____|			
Anticardiolipin antibodies (aCL)	|___|___|____|			
Liver function tests	|___|___|____|			
• alanine transaminase (ALT)	|___|___|____|			
• aspartate transaminase (AST)	|___|___|____|			
• alkaline phosphatase (ALP)	|___|___|____|			
• gamma-glutamyl transpeptidase (GGT)	|___|___|____|			
• total Bilirubin	|___|___|____|			
Ultrasound of joints and tissues	|___|___|____|			
Temporal Artery biopsy	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____||____|_____|	
☐ Resolved with Sequelae	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____|____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

V. Medical History:

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases, *specifically:*				Disease is currently controlled:	
	Yes	No	Date of Diagnosis (dd/mm/yyyy)	Yes	No
• Carpal tunnel syndrome	☐	☐	|_____|_____|_____|	☐	☐
• Temporal arteritis	☐	☐	|_____|_____|_____|	☐	☐
• Other rheumatic diseases (specify)	☐	☐	|_____|_____|_____|	☐	☐

If yes, please describe the course of illness:

6.2 Has the patient previously experienced other immune-mediated/autoimmune disease? Yes ☐ No ☐

If yes, please specify diagnosis and describe the course of the illness:

6.3 Has the patient experienced similar symptoms in the past? Yes ☐ No ☐

If yes, please describe the pattern of progression:

6.4 Does the patient have a history of recent bacterial or viral infection? Yes ☐ No ☐

If yes, please describe the course of the illness and infectious agent:

6.5 Does the patient have a family history of immune-mediated / autoimmune diseases? Yes ☐ No ☐

If yes, please specify the diagnosis and the relationship to the patient (e.g. mother, father, brother…etc.):

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or route of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration	Administration route
SHINGRIX 1st			|_____|_____|_______|	
SHINGRIX 2nd			|_____|_____|_______|	
			|_____|_____|_______|	
			|_____|_____|_______|	

VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details

Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |______|______|_______|	Signature

Targeted Follow–Up Questionnaire Shingrixin and Psoriasis or Psoriatic Arthropathy

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to Psoriasis or psoriatic arthropathy in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***Try to fill this questionnaire as comprehensively as possible***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth: (dd/mm/yyyy) |_____|_____|_____|	Age: (yy.mm) |_____|_____|
Weight/Unit _____/_____		Height / Unit _____/_____	Gender: F ☐ M ☐

II. Description of the Event:

1. **Date of onset symptoms (dd/mm/yyyy):** \|_____\|_____\|_____\|
2. **Clinical sign and symptoms:** *Please tick all that apply. For each sign and symptom, please describe in detail when possible:*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Ongoing Yes	Ongoing No	Stop date (dd/mm/yyyy)	Description
2.1	Dry cracked skin with plaques and/or red patches	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.2	Red, scaly skin rash	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.3	Dactylitis (sausage digits)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.4	Reduced range of motion in the joints, stiffness	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.5	Itching	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.6	Nail changes (pitting, onycholysis, subungual hyperkeratosis) *please specify*	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.7	Distal interphalangeal joint arthritis (specify swollen fingers or toes)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.8	Paronychia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.9	Arthritis mutilans	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.10	Spondylitis	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.11	Enthesitis such as Aquilles tendinitis	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.12	Uveitis							
Other signs/symptoms? please specify:		☐	☐	|__|__|____|	☐	☐	|__|__|____|	

3.0	Provide relevant results of physical examination		
4.0	Prior to receiving the suspected SHINGRIX vaccine, were there similar signs or symptoms noticed?	Yes ☐	No ☐

If yes, please specify:

III. Diagnostic tests:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/Titers	Reference Range
Complete blood count	|___|___|____|			
White blood cell (WBC)	|___|___|____|			
WBC differential	|___|___|____|			
Platelet count	|___|___|____|			
Erythrocyte Sedimentation Rate (ESR)	|___|___|____|			
Serum C-reactive protein (CRP)	|___|___|____|			
Rheumatoid factor (RF)	|___|___|____|			
Anti-nuclear antibodies (ANA)	|___|___|____|			
Skin biopsy	|___|___|____|			
Radiography of affected joints	|___|___|____|			
Synovial fluid analyses	|___|___|____|			
Magnetic Resonance Image (MRI)	|___|___|____|			
Computerized tomography (CT) scan	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____|____|_____|	
☐ Resolved with Sequelae	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____|____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

V. Medical History:

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases or risk factors, *specifically*:				Disease is currently controlled:	
	Yes	No	Date of Diagnosis (dd/mm/yyyy)	Yes	No
• Recent viral or bacterial infection	☐	☐	|_____|_____|_____|	☐	☐
• Skin injury, such as a cut or scrape, a bug bite or a severe sunburn, trama	☐	☐	|_____|_____|_____|	☐	☐
• Stress	☐	☐	|_____|_____|_____|	☐	☐
• Smoking	☐	☐	|_____|_____|_____|	☐	☐
• HIV	☐	☐	|_____|_____|_____|	☐	☐

If yes, please describe the diagnosis and course of illness:

6.2 Has the patient experienced other immune-mediated/autoimmune disease? Yes ☐ No ☐

If yes, please describe the diagnosis and course of the illness:

6.3 Have there been similar symptoms in the past? Yes ☐ No ☐

If yes, please describe the pattern of progression:

6.4 Does the patient have a family history of immune-mediated / autoimmune diseases? Yes ☐ No ☐

If yes, please specify the diagnosis and relationship to the patient (e.g. mother, father, brother… etc.):

`

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or rout of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration	Administration route
SHINGRIX 1st			|_____|_____|________|	
SHINGRIX 2nd			|_____|_____|________|	
			|_____|_____|________|	
			|_____|_____|________|	

VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. For medications specified below, if the patient didn't take it, please leave it blank. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
Lithium			|___|___|____|/|___|___|____|	
Beta blockers			|___|___|____|/|___|___|____|	
Antimalarial drugs			|___|___|____|/|___|___|____|	
Iodides			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	
			|___|___|____|/|___|___|____|	

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details

Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |______|______|_______|	Signature

Targeted Follow–Up Questionnaire
Shingrix and Rheumatoid Arthritis

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to Rheumatoid Arthritis in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***Try to fill this questionnaire as comprehensively as possible***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth: (dd/mm/yyyy) |_____|_____|_____|	Age: (yy.mm) |_____|_____|
Weight/Unit _____/_____		Height / Unit _____/_____	Gender: F ☐ M ☐

II. Description of the Event:

1. **Date of onset symptoms (dd/mm/yyyy):** |_____|_____|_____|
2. **Clinical sign and symptoms:** *Please tick all that apply. For each sign and symptom, please describe in detail when possible:*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Ongoing Yes	Ongoing No	Stop date (dd/mm/yyyy)	Description
2.1	Tender, warm and/or swollen joints	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.2	Synovitis	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.3	Morning joint stiffness	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.4	Unexplained weight loss	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.5	Rheumatoid nodules	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.6	Episcleritis	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.7	Keratoconjunctivitis sicca	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.8	Symmetric arthritis (*specify type and number of joints affected*)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
Other signs/symptoms? please specify:		☐	☐	|__|__|____|	☐	☐	|__|__|____|	

3.0	Provide relevant results of physical examinations	
4.0	Prior to receiving the suspected SHINGRIX vaccine, were there similar signs or symptoms noticed?	Yes ☐ No ☐

If yes, please specify:

III. Diagnostic Tests:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/Titers	Reference Range
Complete blood count	|___|___|____|			
White blood cell (WBC)	|___|___|____|			
WBC differential	|___|___|____|			
Platelet count	|___|___|____|			
Erythrocyte Sedimentation Rate (ESR)	|___|___|____|			
Serum C-reactive protein (CRP)	|___|___|____|			
X-rays (hands and feet)	|___|___|____|			
Anti-cyclic citrullinated peptide (anti-CCP)	|___|___|____|			
Antinuclear antibody (ANA)	|___|___|____|			
Rheumatoid factor (RF)	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____|____|_____|	
☐ Resolved with Sequelae	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____|____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

V. Medical History:

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases, *specifically:*				Disease is currently controlled:	
	Yes	No	Date of Diagnosis (dd/mm/yyyy)	Yes	No
• Amyloidosis disease	☐	☐	|_____|_____|_____|	☐	☐

If yes, please describe the course of illness:

6.2 Has the patient previously experienced other immune-mediated/autoimmune disease? Yes ☐ No ☐

If yes, please specify diagnosis and describe the course of the illness:

6.3 Has the patient experienced similar symptoms in the past? Yes ☐ No ☐

If yes, please describe the pattern of progression:

6.4 Does the patient have history of recent infectious diseases (e.g. bacterial, viral, fungal …)? Yes ☐ No ☐

If yes, please describe course of the illness and infectious agent:

6.5 Does the patient have a significant smoking history? *If yes, how many years?* Yes ☐ No ☐

6.6 Does the patient have a family history of immune-mediated / autoimmune diseases? Yes ☐ No ☐

If yes, please specify the diagnosis and relationship to the patient (e.g. mother, father, brother…etc.):

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or route of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration	Administration route
SHINGRIX 1st			|____|____|______|	
SHINGRIX 2nd			|____|____|______|	
			|____|____|______|	
			|____|____|______|	

VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details

Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |_____|_____|______|	Signature

Targeted Follow–Up Questionnaire
Shingrix and Still's Disease Adult Onset

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to Still's Disease (Adult Onset) in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***Try to fill this questionnaire as comprehensively as possible***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth: (dd/mm/yyyy) |_____|_____|_____|	Age: (yy.mm) |_____|_____|
Weight/Unit _____/_____		Height / Unit _____/_____	Gender: F ☐ M ☐

II. Description of the Event:

1. **Date of onset symptoms (dd/mm/yyyy):** \|_____\|_____\|_____\|
2. **Clinical sign and symptoms**: *Please tick all that apply. For each sign and symptom, please describe in detail when possible:*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Ongoing Yes	Ongoing No	Stop date (dd/mm/yyyy)	Description
2.1	Fever	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.2	Evanescent rash	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.3	Arthralgia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.4	Joint swollen	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.5	Generalized myalgia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.6	Morning stiffness	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.7	Sore throat	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.8	Arthritis of the temporal-mandibular joint	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.9	Other arthritis (*specify location and number of joints affected, symmetrical or asymmetrical?*)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.10	Abdominal pain	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.11	Lymphadenopathy	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.12	Splenomegaly	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.13	Hepatomegaly	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.14	Orthopnea	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.15	Serositis (pleuritis, pericarditis)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.16	Carpal or tarsal ankylosis	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.17	Alopecia	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.18	Uveitis	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.19	Iridocyclitis	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
Other signs/symptoms? please specify:		☐	☐	|__|__|____|	☐	☐	|__|__|____|	

3.0	Provide other relevant results of physical examination:		
4.0	Prior to receiving the suspected SHINGRIX vaccine, were there similar signs or symptoms noticed?	Yes ☐	No ☐
If yes, please specify:			

III. Diagnostic Tests:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/Titers	Reference Range
Complete blood count	|___|___|____|			
White blood cell (WBC)	|___|___|____|			
WBC differential	|___|___|____|			
Platelet count	|___|___|____|			
Erythrocyte Sedimentation Rate (ESR)	|___|___|____|			
Serum C-reactive protein (CRP)	|___|___|____|			
Rheumatoid Factor (RF)	|___|___|____|			
Transaminases (ALT)	|___|___|____|			
Transaminases (AST)	|___|___|____|			
Lactic dehydrogenase	|___|___|____|			
Coagulation tests	|___|___|____|			
Prothrombin time	|___|___|____|			
Partial thromboplastin	|___|___|____|			
Fibrinogen	|___|___|____|			
D-dimer	|___|___|____|			
Urinalysis with microscopic examination	|___|___|____|			
Serum Glycosylated Ferritin	|___|___|____|			
Serum Protein and Albumin	|___|___|____|			
Electrolytes	|___|___|____|			
Antinuclear antibody (ANA)	|___|___|____|			
Streptococcal Group A screen	|___|___|____|			
Antistreptolysin 0 (AS0)	|___|___|____|			
Anti-DNAse B	|___|___|____|			
X-ray of the affected joints	|___|___|____|			
Bone scanning	|___|___|____|			
Magnetic Resonance Image (MRI)	|___|___|____|			
Computerized tomography (CT) scan	|___|___|____|			
Echocardiography	|___|___|____|			
Synovial biopsy	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____|____|_____|	
☐ Resolved with Sequelae	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____|____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

V. Medical History:

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases, *specifically*:				Disease is currently controlled:	
	Yes	No	Date of Diagnosis (dd/mm/yyyy)	Yes	No
• Rheumatic diseases	☐	☐	|___|___|____|	☐	☐
• Inflammatory Bowel Disease	☐	☐	|___|___|____|	☐	☐
• Malignancies	☐	☐	|___|___|____|	☐	☐

If yes, please describe the diagnosis and course of illness:

6.2 Has the patient experienced previously other immune-mediated/autoimmune disease? Yes ☐ No ☐

If yes, please specify diagnosis and describe the course of the illness:

6.3 Has the patient experienced similar symptoms in the past? Yes ☐ No ☐

If yes, please describe the pattern of progression:

6.4 Does the patient have history of a recent bacterial or viral infection? Yes ☐ No ☐

If yes, please describe the course of the illness and infectious agent:

6.5 Does the patient have a family history of immune-mediated / autoimmune diseases? Yes ☐ No ☐

If yes, please specify the diagnosis and the relationship to the patient (e.g. mother, father, brother…etc.):

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or route of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration	Administration route
SHINGRIX 1st			|___|___|____|	
SHINGRIX 2nd			|___|___|____|	
			|___|___|____|	
			|___|___|____|	

VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details	
Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |_____|_____|_____|	Signature

`

Targeted Follow–Up Questionnaire Shingrix and Giant cell arteritis or Temporal Arteritis

SECTION TO BE FILLED BY GSK

GSK Case ID:

SECTION TO BE FILLED BY REPORTER

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to Giant cell arteritis or Temporal Arteritis in a patient following exposure to HZ/su vaccination (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***Try to fill this questionnaire as comprehensively as possible***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should only be completed by a trained healthcare professional***

I. Patient's Details

Patient initials:	Country:	Date of Birth: (dd/mm/yyyy) |_____|_____|_____|	Age: (yy.mm) |_____|_____|
Weight/Unit _____/_____		Height / Unit _____/_____	Gender: F ☐ M ☐

II. Description of the Event:

1. **Date of onset symptoms (dd/mm/yyyy):** |_____|_____|_____|
2. **Clinical sign and symptoms:** *Please tick all that apply. For each sign and symptom, please describe in detail when possible:*

	Sign and/or symptom	Yes	No	Start date (dd/mm/yyyy)	Ongoing Yes	Ongoing No	Stop date (dd/mm/yyyy)	Description
2.1	Facial pain or throbbing headache in the temples	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.2	Sudden vision loss (*specify transient or permanent?*)	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.3	Diplopia or double vision	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.4	Jaw claudication	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.5	Hearing loss	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.6	Unintentional weight loss	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.7	Fatigue	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.8	Weakness or malaise	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.9	Tenderness in the scalp and/or temple areas	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.10	Shoulder pain, hip pain and stiffness	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.11	Fever	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.12	Poor appetite	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.13	Dry cough or sore throat	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.14	Transient ischemic attacks or stroke	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
2.15	Tongue or scalp infarction	☐	☐	|__|__|____|	☐	☐	|__|__|____|	
Other signs/symptoms? Please specify:		☐	☐	|__|__|____|	☐	☐	|__|__|____|	

3.0	Provide relevant results of physical and ophthalmoscopic examination *including blood pressure (Is there a difference of >10 mmHg in systolic blood pressure between arms?), visual acuity, extra ocular movements, intraocular pressure, slit-lamp examination, etc*.
4.0	Prior to receiving the suspected SHINGRIX vaccine, were there similar signs or symptoms noticed? Yes ☐ No ☐
If yes, please specify:	

`

III. Diagnostic Tests:

Please provide all relevant diagnostic test/examination results of abnormal laboratory values / investigations (or provide copies of relevant results) that supporting the diagnosis. Please provide the reference range where applicable.

Examinations	Date of the test	Results	Units/Titers	Reference Range
Complete blood count	|___|___|____|			
White blood cell (WBC)	|___|___|____|			
WBC differential	|___|___|____|			
Platelet count	|___|___|____|			
Hemoglobin	|___|___|____|			
Hematocrit	|___|___|____|			
Erythrocyte Sedimentation Rate (ESR)	|___|___|____|			
Serum C-reactive protein (CRP)	|___|___|____|			
Temporal Artery biopsy	|___|___|____|			
Computerized tomography angiography (CTA)	|___|___|____|			
Magnetic resonance angiography (MRA)	|___|___|____|			
Magnetic Resonance Image (MRI)	|___|___|____|			
Computerized tomography (CT) scan	|___|___|____|			
Arteriography, artery color duplex ultrasonography	|___|___|____|			
Anti-neutrophil cytoplasmic antibodies (ANCAs)	|___|___|____|			
Rheumatoid factor (RF)	|___|___|____|			
Alkaline phosphatase (ALT)	|___|___|____|			
Aspartate transaminase (AST)	|___|___|____|			
Any other relevant/abnormal test results, please specify:	|___|___|____|			

IV. Outcome of the event:

☐ Resolved	5.1 *Date of resolving*: |____|____|_____|	
☐ Resolved with Sequelae	5.2 *Please specify*:	
☐ Event is till ongoing		
☐ Unknown		
☐ Fatal	5.3 Date of death: |____|____|_____|	5.4 Cause(s) of death:
	5.5 Was an autopsy performed : Yes ☐ No ☐	5.5.1 Result:

`

V. Medical History:

Describe the patient's relevant medical conditions (current and past), family history and risk factors

6.1 Does the patient have a current or past medical history of other diseases, *specifically*:

	Yes	No	Date of Diagnosis (dd/mm/yyyy)	Disease is currently controlled: Yes	No
• Polymyalgia rheumatica	☐	☐	|____|____|______|	☐	☐
• Optic ischemic neuropathy	☐	☐	|____|____|______|	☐	☐
• Transient ischemic attacks/stroke	☐	☐	|____|____|______|	☐	☐
• Erythema nodosum	☐	☐	|____|____|______|	☐	☐

If yes, please describe the course of illness:

6.2 Has the patient experienced previously other immune-mediated/autoimmune disease? Yes ☐ No ☐

If yes, please specify diagnosis and describe the course of the illness:

6.3 Has the patient experienced similar symptoms in the past? Yes ☐ No ☐

If yes, please describe the pattern of progression:

6.4 Does the patient have history of a recent infection (e.g. spirochetes, Mycobacterium tuberculosis, streptococcal, etc.?) Yes ☐ No ☐

If yes, please describe the course of the illness and the infectious agent:

6.5 Does the patient have a family history of immune-mediated / autoimmune diseases? Yes ☐ No ☐

If yes, please specify the diagnosis and relationship to the patient (e.g. mother, father, brother…etc.):

VI. Relevant Vaccination History

Please insert below details of SHINGRIX vaccine(s) and all known vaccines which were administered to the patient during the last 6 months prior to the onset of symptoms. If you don't know one of the requested details (trade name, batch number, or date or route of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration	Administration route
SHINGRIX 1st			|____|____|______|	
SHINGRIX 2nd			|____|____|______|	
			|____|____|______|	
			|____|____|______|	
			|____|____|______|	

VII. Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the last 6 months prior and during the course of symptoms. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Medications	Dose	Freq/Route	Start date / End date	Indications
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	
			|__|__|___|/|__|__|___|	

`			|___|___|____|/|___|___|____|	

`

VIII. Additional relevant information

Please insert below any relevant information (medical history, clinical details, laboratory diagnosis) you consider of relevance for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

IX. Reporter's Details

Name	Mobile number
Profession	Specialization (if applicable)
Date of the report (dd/mm/yyyy): |_____|_____|_____|	Signature

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

Herpes zoster vaccine & Vaccination Failure/Lack of Efficacy

SECTION TO BE FILLED BY GSK

GSK Case ID: **GSK vaccine name:**

INSTRUCTIONS:

- ***This questionnaire is designed to identify potential factors linked to a reported lack of efficacy in a patient vaccinated with Herpes Zoster vaccine (Shingrix)***
- ***Please read carefully the questions and reply with the facts to the best of your knowledge***
- ***It is recommended you have the patient's file at hand when you fill in this questionnaire***
- ***This questionnaire should be completed by a trained healthcare professional***

Patient initials:	**Country:**	**Date of Birth:** (dd/mm/yyyy) |____||____||_____|	**Age:**	**Gender:** F ☐ M ☐
Weight (kg):	**Date(s) of vaccination:**	**Date of symptom onset:**		**Lot number(s):**

Description of the Event:

COURSE OF ILLNESS

1. Did the patient experienced any of the following: *(please tick all that apply)*

a. Prodromal symptoms (e.g. headache, photophobia) ☐
b. Dermatomal Pain (acute or prolonged) ☐
c. Dermatomal Rash ☐
d. Dermatomal Pain without Rash ☐
e. Itching ☐
f. Altered sensitivity to touch ☐
g. Other symptoms ☐
Please specify: _____

2. Patient was hospitalized Yes ☐ No ☐

→If answered yes, please indicate:

Date of admission (dd/mm/yyyy): |____||____||_____|
Date of discharge (dd/mm/yyyy): |____||____||_____|

3. Diagnosis of Herpes Zoster (Shingles) was confirmed Yes ☐ No ☐

→If answered yes, please specify final diagnosis:

a. Classical Herpes Zoster (unilateral, involving no more than three adjacent dermatomes) ☐
b. Disseminated Herpes Zoster (bilateral OR involving more than three OR non-adjacent dermatomes) ☐
c. Herpes zoster sine herpete (dermatomal distribution pain without rash) ☐

→If answered no, please specify the final diagnoses of the patient:

4. Can the location of the specific affected dermatome(s) be provided? *If yes, please list them below:*	**Yes** ☐	**No** ☐

When available and if consented by the patient, please attach visual evidence of the affected dermatomes to this questionnaire

5. Were any complications of HZ present or specific organ system involvement? (e.g. PHN or post-herpetic neuralgia, Herpes Zoster vasculitis, disseminated disease, ophthalmic disease, neurologic disease, visceral disease, etc.) *If yes, please describe:*	**Yes** ☐	**No** ☐

6. Outcome of the event:

Resolved ☐ → *please specify date of last symptoms:* |____||____||_____|

Resolved with Sequelae ☐ → *please specify*:_____

Resolving ☐

Unresolved ☐

Unknown ☐

Fatal ☐ →*Please specify:*

a. Date of death: |____||____||_____|

b. Was an autopsy performed? Yes ☐ No ☐

→*If an autopsy was performed:*

Date |____||____||_____

Result: _____

c. Cause(s) of death (as reported in death certificate if possible):

	Event	Date of onset
Immediate cause	_____	_____
Underlying cause(s)	_____	_____
	_____	_____
	_____	_____

Other significant conditions contributing to death:

_____

Diagnostic Tests: Please attach all applicable and provide dates for all results

Please provide a summary of main results of abnormal laboratory values / investigations* (or provide copies of relevant results):**

***** Relevant laboratory findings include VZV-positive polymerase chain reaction (PCR), culture, immunohistochemical staining, or other tests that strongly suggest VZV infection, which have been performed in the course of a medical evaluation.**

History of Herpes Zoster

Past Medical history (especially, history of a condition or medication that may result in immunosuppression):

Are you aware of any prior episodes of herpes zoster in this patient *(please tick one)*?

Prior shingles history unknown ☐
This is the first shingles episode ☐
History of prior shingles episodes ☐

Did patient previously experience Primary Herpes Zoster (Chickenpox) *(please tick one)*?

Yes ☐
No ☐
Does not remember ☐

Please list any other medications that may have contributed to shingles/herpes zoster, if not already provided:

Vaccination History

Please insert below all known vaccines against which were administered to the patient prior to the onset of symptoms. Special interest is on vaccines against Herpes Zoster Virus. If you don't know one of the requested details (trade name, batch number, or date of administration), please write "UNK" instead.

Trade name	Batch n°	Dose number	Date of administration

Concomitant medication (including over-the counter medications)

Please insert below all medications given to the patient during the course of symptoms. If you don't know one of the requested details (trade name, freq/route, start date/end date), please write "UNK" instead

Trade Name	Dose	Freq/Route	Start date / End date	Reason for medication
			/	
			/	
			/	
			/	
			/	
			/	
			/	

Additional relevant information

Please insert below any relevant information you consider medically relevant for this case not previously described in the sections above

Additional relevant information (not described elsewhere)

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Not applicable.