Amsterdam, 16 October 2025
EMADOC-1700519818-2471078
Committee for Medicinal Products for Human use (CHMP)

Assessment report on extension of marketing authorisation.

Shingrix

Common name: Herpes zoster vaccine (recombinant, adjuvanted)

Procedure No. EMA/X/0000243671

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Shingrix
MAH	GlaxoSmithKline Biologicals Rue de l'Institut 89 1330 Rixensart Belgium
Active substance:	Varicella Zoster Virus glycoprotein E antigen (gE) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology, adjuvanted with $AS01_B$ containing: plant extract *Quillaja saponaria* Molina, fraction 21 (QS 21), 3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota*
International Non-proprietary Name/Common Name:	Herpes zoster vaccine (recombinant, adjuvanted)
Pharmaco-therapeutic group (ATC Code):	Varicella zoster vaccines (J07BK03)
Therapeutic indication(s):	Shingrix is indicated for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in: • adults 50 years of age or older; • adults 18 years of age or older at increased risk of HZ. The use of Shingrix should be in accordance with official recommendations.
Pharmaceutical form(s):	Suspension for injection
Strength(s):	One dose (0.5 mL) contains: Varicella Zoster Virus glycoprotein E antigen, (50 micrograms) adjuvanted with $AS01_B$ containing: plant extract *Quillaja saponaria* Molina, fraction 21 (QS 21) (50 micrograms) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella Minnesota* (50 micrograms)
Route(s) of administration:	Intramuscular use
Packaging:	pre-filled syringe
Package size(s):	1 pre-filled syringe 10 pre-filled syringes

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List of abbreviations

AS	active substance
$AS01_B$	Adjuvant System containing 50 µg MPL, 50 µg QS-21 and liposomes
CHMP	Committee for Medicinal Products for Human Use
CPP	critical process parameters
DOPC	Dioleoyl Phosphatidylcholine
EMA	European Medicines Agency, EU
ERA	Environmental Risk Assessment
EU	European Union
FB	final bulk
FC	final container
FP	finished product
gE	Glycoprotein E
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
HZ	Herpes Zoster
ICH	International Conference on Harmonization
L	litre
MCB	master cell bank
MPL	3-O-desacyl-4'-monophosporyl Lipid A
PFS	pre-filled syringe
Ph. Eur.	European Pharmacopoeia
PM	in process monitoring
PP	process parameters
PPQ	process performance qualification
PS80	polysorbate 80
QA	quality attributes
QC	quality control
QD	quality decision
QS-21	Quillaja saponaria Molina fraction 21
RV	reconstituted vaccine
TSE	transmissible spongiform encephalopathy
VZV	Varicella Zoster Virus
WCB	working cell bank
WFI	water for injection

1. Background information on the procedure

1.1. Submission of the dossier

GlaxoSmithKline Biologicals submitted on 19 December 2024 an extension of the marketing authorisation to introduce a new pharmaceutical form: suspension for injection (injection).

Furthermore, the PI is brought in line with the latest QRD template version 10.4

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (d) - Extensions of marketing authorisations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0328/2024 on the granting a product-specific waiver for a paediatric fully liquid formulation.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. Scientific Advice

The MAH had two follow-up Scientific Advice with EMA (EMA/SA/0000079850 dated 19/05/2022 and EMA/SA/0000173718 dated 19/09/2024) on the approach to demonstrate comparability between the current authorised and the proposed fully liquid Shingrix vaccine, and to support gE/AS01$_B$ Liquid vaccine registration. In summary, the CHMP agreed that appropriate technical comparability study data may be supportive of the licensure of gE/AS01$_B$ Liquid form and agreed that if comparability can be shown by analytical tools, there is no need for clinical (bridging) study.

The Application is also supported by new nonclinical data. No clinical data were submitted. The existing clinical package supporting the current approved pharmaceutical form of Shingrix is adequate to support the new liquid form of the vaccine (gE/AS01$_B$ Liquid vaccine).

1.5. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christophe Focke

The application was received by the EMA on	19 December 2024
The procedure started on	23 January 2025
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 April 2025
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	N/A
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 April 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 May 2025
The CHMP agreed on the consolidated List of Questions to be sent to GlaxoSmithKline Biologicals during the meeting on	22 May 2025
GlaxoSmithKline Biologicals submitted the responses to the CHMP consolidated List of Questions on	14 August 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	22 August 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Shingrix on	16 October 2025

2. Scientific discussion

2.1. Problem statement

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

• adults 50 years of age or older;

• adults 18 years of age or older at increased risk of HZ.

The currently approved pharmaceutical form, referred to as 2-vial gE/AS01$_B$, is supplied as a single-dose vial of the lyophilized glycoprotein E (gE) antigen component (50 µg) to be reconstituted with the accompanying vial of the AS01$_B$ adjuvant suspension component (50 µg MPL, 50 µg QS-21).

With this Line Extension, the MAH is seeking licensure of a new fully liquid pharmaceutical form (gE/AS01$_B$ Liquid) as an additional form to the approved Shingrix vaccine (2-vial gE/AS01$_B$). The gE/AS01$_B$ Liquid vaccine has the same composition and is indicated for the same adult populations as the currently approved Shingrix (2-vial gE/AS01$_B$). The proposed gE/AS01$_B$ Liquid vaccine will be presented in a pre-filled syringe.

2.1.1. Disease or condition

Herpes zoster (HZ), commonly known as shingles, is characterised by a vesicular rash accompanied by acute pain in the region of the affected dermatome. The disease results from reactivation of the varicella zoster virus (VZV). A primary infection with VZV is a prerequisite for developing HZ. During the primary varicella infection (chickenpox), the varicella virus will travel along sensory neurons to

dorsal root ganglia and establish lifelong latency. Following a variable period of latency, VZV can reactivate to produce infectious virus. This virus can travel to the skin along the neuron axon and produce a painful HZ rash. Patients experience significant pain and discomfort that may last for weeks, months or even years in severe cases, diminishing the quality of life. HZ is thought to be associated with a decline in cell mediated immunity due to aging or to an immunosuppressive illness or treatment. The lifetime risk of HZ is estimated to be 10-30%. Mortality rates associated with HZ ranged from 0.01 to 0.46 per 100,000 persons-years and the majority of deaths occurred in adults ⩾ 60 years of age (Kawai 2014).

2.1.2. Epidemiology and risk factors

More than 90% of adults have been infected with VZV and are, therefore, at risk of developing HZ.

The overall incidence rate of HZ in Europe, North America and Asia-Pacific is about 3 to 5 cases per 1000 person-years (Kawai 2014).

The most common complication of HZ is postherpetic neuralgia (PHN), defined as pain that persists beyond 90 days after the onset of the zoster rash. This pain is often chronic and debilitating and difficult to treat effectively. About 5 to 30% of people who get HZ will experience PHN (depending of the type of study design and age distribution of study populations). Other less frequent HZ complications include HZ ophthalmicus (HZO) which occurs in 10% to 15% of HZ patients (Kawai 2014).

The incidence and severity of HZ disease increase with age, with an exponential increase in incidence after the age of 50 years, which correlates with ageing-related decline in cell-mediated immunity. Two-thirds of HZ cases are occurring in adults ⩾ 50 YOA (Yawn 2007, Kawai 2014). Epidemiological evidence confirms that the risk of HZ increases dramatically in adults ⩾18 YOA who are immunodeficient or immunosuppressed due to disease or therapy, placing them at a risk comparable to and in many instances far exceeding the risk seen in the general adult population ⩾50 YOA (O'Connor 2013). Immunocompromised (IC) individuals are not only at increased risk for the development of HZ but also develop more severe HZ than immunocompetent person, including persistent post-HZ pain and PHN complications. Beside immunosuppression, many chronic conditions such as diabetes, asthma, COPD, cardiovascular diseases, renal diseases are associated with an increased risk of HZ (Kawai 2017, Marra 2020).

2.1.3. Clinical presentation, diagnosis

Herpes zoster (HZ) is the reactivation of a viral infection caused by the same virus that causes chickenpox as primary infection (varicella-zoster virus, VZV). After the primary infection, the virus migrates to the central nervous system, where it establishes latency in sensory neurons of cranial and dorsal root ganglia. Following a variable period during which it remains latent, it can reactivate later in life to cause HZ. HZ typically presents as an acute, painful, vesicular eruption distributed along a single dermatome. During the eruptive phase, acute local neurological pain occurs in up to 90% of immunocompetent individuals. The prodromal phase is typically 3-4 days in duration, but longer durations of ≥ 1 week are not uncommon. Fever, malaise and headache may be present. The rash typically heals in 2-4 weeks but may leave scaring and pigmentation changes. The median duration of acute pain is 2 weeks. Post-herpetic Neuralgia (PHN) is the most common severe complication of HZ and can last for weeks, months or even years. PHN is a complex neuropathic pain condition which is a consequence of the 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 herpes zoster rash. Other less frequent complications of HZ include HZ Ophthalmicus (e.g. keratitis, retinitis, glaucoma, optic neuritis), Ramsay Hunt Syndrome

(HZ oticus), central nervous system complications (such as VZV encephalitis, meningitis, myelitis). Disseminated zoster (> 20 skin lesions outside a single dermatome), secondary bacterial infection with Staphylococcus aureus and, rarely, purpura and necrosis are also reported.

2.1.4. Management

Treatment

The primary treatment for shingles involves antiviral medications, such as acyclovir, valacyclovir, or famciclovir. These medications can help to reduce the severity and duration of the illness as well as to reduce the risk of complications. Antiviral medications are most effective if started within 72 hours of the rash appearing.

Other treatments include pain relievers such as ibuprofen or acetaminophen (paracetamol). In some cases, stronger pain medications, such as opioids or nerve pain medications, may be prescribed. Calamine lotion or cool compresses can also be used.

Prophylaxis

A live-attenuated VZV vaccine (Zostavax,Merck & Co) was authorised in 2006 in the EU for use in immunocompetent adults ⩾50 YOA to prevent HZ and PHN. This vaccine was contraindicated in immunosuppressed or immunodeficient individuals due to concerns of possible vaccine-associated disseminated disease. On 1 June 2025, the European Commission withdrew the marketing authorisation for Zostavax (shingles (herpes zoster) vaccine (live)) in the European Union (EU). The withdrawal was at the request of the marketing authorisation holder, Merck Sharp & Dohme B.V., which notified the European Commission of its decision to permanently discontinue the marketing of the product for commercial reasons.

Shingrix is indicated for prevention of HZ and PHN, in (i) adults 50 years of age or older and (ii) adults 18 years of age or older at increased risk of HZ. The only contraindication of Shingrix is hypersensitivity to the active substances or to any of the excipients of the vaccine.

Unmet medical need

Shingrix was developed to address the medical need to prevent HZ and HZ-related complications such as PHN in older adults ⩾50 YOA and in IC adults ⩾18 YOA.

As summarized above, epidemiological evidence indicates that adults ⩾ 50 YOA are at increased risk of HZ, as well as adults ⩾18 YOA with underlying medical conditions or treatments predisposing them to HZ. This includes patients chronically using immunosuppressive medications (e.g., oncology patients and transplant recipients), patients with autoimmune diseases or other relevant chronic conditions (e.g., rheumatoid arthritis, IBD, COPD, cardiovascular diseases, renal disease, systemic lupus erythematosus, asthma, Type 2 diabetes mellitus, HIV), as well as subjects with congenital immunodeficiencies. This wide spectrum of IC/conditions altering the immune status in adults illustrates the medical need for prevention through vaccination.

2.2. About the product

Shingrix was approved for the first time on 13 October 2017 in Canada. In the EEA, Shingrix was granted marketing authorization in March 2018. The currently registered pharmaceutical form is a lyophilized powder (antigen) and suspension (adjuvant) for suspension for injection (referred as 2-vial gE/AS01$_B$).

The vaccine is currently indicated for the prevention of HZ and PHN in adults ⩾50 YOA, and in adults ⩾18 YOA at increased risk of HZ.

Shingrix is currently approved in over 70 countries in different geographical regions.

The vaccine components include recombinant VZV surface gE antigen (50 µg/dose) and the $AS01_B$ adjuvant system. The vaccine was designed to induce strong cellular and humoral immune responses in individuals who are at increased risk of developing HZ. The antigen component of Shingrix is the recombinant VZV surface gE produced in CHO cells. One 0.5 mL dose of the vaccine contains 50 µg of gE protein. The adjuvant system is $AS01_B$, which consists of 50 µg QS-21, 50 µg MPL, and liposomes.

Shingrix has demonstrated >90% efficacy in preventing HZ in adults ⩾50 YOA, including the subpopulation of adults aged 70 years and older (over a median follow-up of 3.1 years and 4.0 years, respectively). VE against PHN was also high (>88%) for both age category. In autologous haematopoietic stem cell transplant recipients ⩾18 YOA, Shingrix efficacy against HZ was 68% (over a median follow-up of 21 months) and in an immunocompromised adult population with haematological malignancies the efficacy was 87% (over a median follow-up of 11.1 months, *post-hoc* analysis).

The MAH developed a new formulation of Shingrix, referred as gE/$AS01_B$ Liquid vaccine, resulting from the co-formulation of the Shingrix gE antigen (no longer lyophilised) and adjuvant components, with the same composition as the current 2-vial gE/$AS01_B$. The gE/$AS01_B$ Liquid presentation is a single container pre-filled syringe. gE/$AS01_B$ Liquid is indicated for the same adult population as currently approved for 2-vial gE/$AS01_B$.

The MAH anticipated that the benefit-risk profile of the gE/$AS01_B$ Liquid vaccine is comparable to the benefit risk profile of the currently approved lyophilised presentation (gE/$AS01_B$) provided demonstration of the comparability at quality level of the currently approved gE/$AS01_B$ vaccine with the gE/$AS01_B$ Liquid vaccine.

2.3. Type of Application and aspects on development

2.4. Quality aspects

2.4.1. Introduction

Shingrix liquid vaccine, also referred to as gE/$AS01_B$ liquid vaccine, is a preservative-free suspension for intramuscular injection intended for the prevention of Herpes Zoster (HZ) and HZ-related complications. The vaccine contains the Varicella Zoster Virus (VZV) glycoprotein E (gE) antigen formulated with the $AS01_B$ Adjuvant.

The current application concerns a line extension to the already registered 2-vial presentation of Shingrix vaccine with a lyophilised gE antigen and a liquid adjuvant system.

The finished product (FP) is presented as a 0.5 ml suspension for injection in pre-filled syringe containing 50 micrograms of Varicella Zoster Virus glycoprotein E antigen as active substance (AS).

Other ingredients are: sucrose, polysorbate 80, sodium dihydrogen phosphate dihydrate, dipotassium phosphate, 3-O-desacyl-4'- monophosphoryl lipid A (MPL), Purified Quillaja Saponin (QS-21), dioleoyl phosphatidylcholine, cholesterol, sodium chloride, disodium phosphate anhydrous, potassium dihydrogen phosphate, water for injections.

The product is available in pre-filled syringes (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap in pack sizes of 1 and 10 syringes without needles.

2.4.2. Active Substance

The active substance of the fully liquid Shingrix vaccine presentation (current application, line extension) is identical to the active substance of the currently registered lyophilised presentation of Shingrix vaccine.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Shingrix liquid vaccine, also referred to as gE/AS01$_B$ liquid vaccine, is a preservative-free suspension for intramuscular injection intended for the prevention of Herpes Zoster (HZ) and HZ-related complications. The vaccine contains the Varicella Zoster Virus (VZV) glycoprotein E (gE) antigen formulated with the AS01$_B$ Adjuvant. gE/AS01$_B$ Liquid is a ready-to-use liquid suspension for injection appearing opalescent, colourless to pale brownish presented in prefilled syringes (PFS). The volume per nominal dose is 0.5 mL. The composition of the gE/AS01$_B$ Liquid Final Container per nominal dose (0.5 mL) is presented in Table 1 below. All excipients used in the finished product (FP) are of compendial grade (compliant with Ph. Eur), except QS-21 and DOPC. Specifications for QS-21 and DOPC have been provided and are considered acceptable and properly justified.

Table 1 Nominal Composition of the gE/AS01$_B$ Liquid Final Container (PFS)

Ingredients[2]	**Quantity (per 0.5 mL Dose)**[1]	**Function**	**Reference/ Monograph Standard**
gE	50 µg	Antigen	In house
3-O-desacyl-4'-monophosphoryl lipid A (MPL)	50 µg	Immuno-enhancer	*Ph. Eur.* 2537
Purified Quillaja Saponin (QS-21)[3]	50 µg	Immuno-enhancer	In house
Water for injection (WFI)	*q.s. ad* 0.5 mL	Solvent	*Ph. Eur.* 0169, USP, JP

1. gE/AS01$_B$ Liquid Final Container lots are overfilled to guarantee an effective dose of 0.5 mL.
2. Other excipients include dioleoyl phosphatidylcholine (DOPC)(a liposome membrane constituent), cholesterol (a liposome membrane constituent and used for quenching of QS-21 haemolytic activity), sucrose, polysorbate 80 (for protein solubilisation and recovery), sodium chloride (a tonicity agent), sodium dihydrogen phosphate dihydrate (a buffering agent), dipotassium phosphate (a buffering agent), disodium phosphate anhydrous (a buffering agent), potassium dihydrogen phosphate (a buffering agent). All these excipients comply with Ph.Eur. In the absence of a respective Ph.Eur. monograph for DOPC, an in-house specification applies.
3. Purified *Quillaja Saponin* Fraction 21 is the full name of QS-21.

With respect to the formulation development, the composition of the liquid formulation was justified. An identical composition was chosen with the same excipients (same composition) as in the currently registered 2-vial Shingrix vaccine (with lyophilised gE component and a separate liquid AS01$_B$ adjuvant) in order to avoid the need for additional clinical studies. A comparability assessment was performed which showed that Shingrix liquid vaccine is comparable to the 2-vial Shingrix vaccine.

The main objective of developing a gE/AS01$_B$ liquid formulation (as compared to the currently registered 2-vial vaccine) is to increase manufacturing capacity due to high demand, easier handling of administration and lower costs for storage and shipment.

Both glass vial and pre-filled syringe (PFS) presentations have been evaluated for gE/AS01$_B$ liquid vaccine; the PFS presentation was chosen since the product quality and stability in the PFS is comparable to the vial presentation.

No overage is used for the manufacturing of the gE/AS01$_B$ liquid at the formulation step however, the target fill volume includes an overfill to compensate for liquid loss for dead volume remaining in the needle and syringe barrel following administration of the vaccine. The overfill ensures a nominal injection volume of 0.5 mL.

An overview of the manufacturing changes induced by the switch from a 2-vial gE/AS01$_B$ product to a gE/AS01$_B$ liquid pre-filled syringe (PFS) is provided by the applicant. The changes relate to the manufacturing process at the finished product level only. The manufacturing of both active substance and adjuvant system components remains the same as for the 2-vial gE/AS01$_B$ formulation.

In principle, the analytical methods used for Quality Control (QC) release testing of the gE/AS01$_B$ liquid final container (FC) are the ones that are also used for release testing of the gE purified bulk (PB), gE FC, AS01$_B$ FC and characterisation of the gE/AS01$_B$ reconstituted vaccine (RV). There are a few exceptions. Some methods have been either adapted to account for the new matrix or developed specifically for testing of quality attributes of the gE/AS01$_B$ liquid FC. The changes of the analytical methods were described and justified.

As regards the container closure system, the syringe is composed of a syringe barrel, with a Luer Lock closure system and a rubber tip cap. The syringe component suppliers are specified. Sufficient sterilisation details have been provided. It was demonstrated that the syringe is compatible with the gE/AS01$_B$ liquid vaccine formulation.

The applicant also assessed the compatibility between the components of gE/AS01$_B$ liquid vaccine. Stability data indicate that PS80 in the gE/AS01$_B$ liquid vaccine is able to prevent gE protein aggregation.

2.4.3.2. Manufacture of the product and process controls

The name and address of the manufacturer involved in the manufacture and testing of the finished product (FP) is GlaxoSmithKline Biologicals s.a., Parc de la Noire Epine, Avenue Fleming 20, 1300 Wavre, Belgium. The QA release of the final product is performed by GlaxoSmithKline Biologicals s.a., Rue de l'Institut 89, 1330 Rixensart, Belgium. All sites have valid GMP certificates. An example of a batch formula is provided.

A description of the manufacturing process of the gE/AS01$_B$ liquid vaccine is provided. For the formulation, all ingredients were added in sufficient amounts to reach the target concentration and mixed. The gE/AS01$_B$ final bulk is sterile filtered and the sterile final bulk (FB) is aseptically filled in syringes.

In general, the description of the manufacturing process is acceptable and sufficiently detailed.

Process controls are applied during the manufacturing process and are classified in two categories: In-process quality decision (QD) tests and In-process monitoring (PM) tests. These tests are used to evaluate process consistency and for data accumulation.

Consecutive gE/AS01$_B$ FB PPQ runs of a specified number of batches have been successfully completed. This is acceptable. The assessment of comparability between gE/AS01$_B$ liquid PPQ lots and reference lots (currently registered 2-vial vaccine) has been executed by the applicant and was performed in

accordance with ICH Q5E. It can be concluded that Shingrix FL is comparable to the currently licensed 2-vial Shingrix vaccine.

For the final container, the results of Quality Release, Quality Decision and Characterisation tests are reported. All PPQ runs have been performed under representative conditions. All results of the PPQ runs are within the acceptance criteria. Also, the holding time of the formulated bulk was properly validated as well as the aseptic filling (using media simulation fills).

The gE antigen is also known to be prone to methionine oxidation. The company has demonstrated the absence of potential impact on gE structure and thus immunogenicity. The company has committed to provide methionine oxidation release test results, post-approval- **recommendation 1**.

2.4.3.3. Product specification

The proposed specifications include appropriate physicochemical test and tests for identity, potency and purity. These are deemed suitable and are similar to the ones approved for the 2-vial Shingrix vaccine. Justifications were provided for the specification acceptance limits which are deemed acceptable.

Descriptions are provided for the analytical methods. All methods are properly validated and in-house methods have been validated according to ICH guidance. Methods that are identical to the ones used for release testing of the 2-vial Shingrix vaccine have been validated previously. New methods or methods that were modified (to accommodate the different matrix of the fully liquid Shingrix vaccine) were revalidated.

Batch data were provided for a specified number of FP (PPQ) batches, including full batch scale; all test results complied with the specifications. Also, impurities have been described. A risk assessment has been performed for possible nitrosamine contamination; the evaluation showed that the risk is negligible to non-existent. The company has also performed a risk assessment for elemental impurities (in accordance with ICH Q3D and Ph. Eur. general chapter 5.20) which showed that the risk can be considered negligible.

Reference standards have been described. All reference standards were adequately documented and have been properly qualified. Also, protocols have been provided for qualification of future standards. The qualification protocols are deemed acceptable. It is agreed that future reference standards may be implemented without submitting a variation if they are qualified according to these protocols.

The container closure of the FP is a glass syringe with butyl rubber plunger stopper. All components comply with the respective Ph. Eur. monographs. The container components were described in detail and specifications were provided.

2.4.3.4. Stability of the product

A 36-month shelf-life is proposed when the product is stored in a refrigerator (2 °C – 8 °C).

Stability studies have been performed at long term storage conditions and accelerated conditions on 3 small scale developmental FP lots. In addition, similar stability studies were initiated on the PPQ FP lots. Also, temperature cycling studies have been initiated.

Thus far, 30 months stability data are available from the long-term studies on developmental FP lots. All results comply with the specifications. The FP also remains within specifications after 1 month storage at 37°C and after 6 months storage at 25°C. Furthermore, also results are available from temperature excursion studies during which vaccine is stored at 2-8°C for 6 months and then exposed to 25° for 14 days or 30 days and then put back at 2-8°C for further storage. Results from the 30 month time point are all compliant with the specifications. These results are also highly similar to those of the long term

stability study, indicating that a 4 week exposure to 25°C does not impact the vaccine's stability and further confirming that the liquid presentation of Shingrix vaccine is also relatively stable.

Although the stability data up to 30 months were generated from small scale developmental FP lots, it is agreed that these lots can be considered as representative of the commercial product (as confirmed by the release and characterisation data). The FP production scale is unlikely to impact the stability profile. This is also confirmed by the accelerated stability data which are very similar for the small-scale FP lots and the PPQ FP lots.

Moreover, available results from temperature cycling studies show that a 2 or 4-week period with exposure to 25°C during the long term storage period does not impact the stability of the FP as the stability test results are highly similar to those of the long term FP stability studies (without temperature cycling); no decrease in potency is observed. Importantly, it was shown that the newly available stability data (24m and 30m) all fit within the prediction ranges of the proposed stability model.

Based on the totality of the data available, it is agreed that the stability model proposed by the applicant can be used to support an extension of the stability period supported by the available real-time long-term stability data (up to 30 months) with an additional 6 months. The applicant is, however, requested to provide the final stability data of the PPQ FP batches when the stability studies have been finalised (**recommendation 2**).

The product is to be administered as soon as possible after being removed from the refrigerator. However, stability data indicate that Shingrix is stable for 72 hours at temperatures between 8 °C and 37 °C. At the end of this period Shingrix should be used immediately or discarded. The Product Information states that these data are intended to guide healthcare professionals in case of temporary temperature excursion only.

Photostability was characterized during vaccine development and showed that the quality of Shingrix liquid is not impacted by exposure to light. A follow-up photostability study in accordance with ICH Q1B confirmed that the vaccine is not sensitive to light as no changes were observed in the quality parameters assessed

Based upon the data provided, the initially proposed FP shelf life of 36 months (when stored at 2-8°C) for Shingrix liquid vaccine is deemed acceptable.

2.4.3.5. Post approval change management protocol(s)

The applicant has proposed 2 post-approval change management protocols (PACMP): to implement an additional FP manufacturing site, and a second one to implement 'point of fill sterile filtration'. Both PACMPs provide details on the proposed changes as well as on the validation approach. The acceptance criteria for the CPPs and process parameters are the same as those for the original site. The comparability analysis will be similar (identical criteria) as the one performed to demonstrate comparability between the liquid Shingrix vaccine and the 2-vial Shingrix (with lyophilised gE). Both PACMPs are deemed acceptable. It is agreed that the changes can be implemented via an implementing type IB Variation that contains the results of the process validation and the comparability analysis.

2.4.3.6. Adventitious agents

The strategy used to ensure that the VZV gE active substance and the resulting Shingrix finished product are free of adventitious agents is in compliance with the relevant EU viral safety and TSE requirements and includes: control of raw materials; testing of the MCB and WCB, as well as end of production cells; in-process testing of harvest for adventitious agents and bacterial contamination and viral clearance validation studies.

Raw materials of human or animal origin were used for the first steps of cell bank system development (up to the pre-Master cell bank). A satisfactory evaluation of adventitious agents has been provided for these. The risk of TSE contamination is considered negligible due to the origin of the raw materials. The risk of other adventitious agent contamination is considered limited due to the process steps.

Animal/ human origin materials were not used directly for the manufacture of MCB/WCB but have been used in the manufacture of media components:

- MCB: bovine trypsin -TSE certificate provided, porcine-derived carboxypeptidase B, both used in a cell culture ingredient's manufacture.
- WCB: pepticase from bovine milk, beef peptone and beef extract- TSE certificates provided, porcine trypsin and L-threonine methyl ester (from porcine gelatin and avian feathers) all used in a cell-culture supplement's manufacture.

The TSE risk for these is considered negligible due to the origin of these materials and the TSE certificates, where applicable. The risk of other adventitious agent contamination is considered limited due to the process steps.

With the exception of casamino acids, which are used during the production process of MPL (AS01 Adjuvant System), no materials from human or animal origin are used in the manufacturing process of AS or FP. This source of casamino acids is compliant with current EU TSE guidelines.

The AS manufacturing process contains various steps that were shown to contribute to virus removal/inactivation: chromatography steps, low pH, and viral filtration. Virus removal/inactivation was properly validated in appropriate scale-down models using relevant model viruses. The results confirm that the purification process has an adequate viral clearance capacity. In combination with the testing of starting materials and intermediates this viral clearance capacity reduces the risk of viral contamination to a very low and acceptable level.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Shingrix liquid vaccine, also referred to as gE/AS01$_B$ liquid vaccine, is a preservative-free suspension for intramuscular injection intended for the prevention of Herpes Zoster (HZ) and HZ-related complications. The vaccine contains the Varicella Zoster Virus (VZV) glycoprotein E (gE) antigen formulated with the AS01$_B$ Adjuvant. The current application concerns a line extension to the already registered 2-vial presentation of Shingrix vaccine with a lyophilised gE antigen and a liquid adjuvant system.

The pharmaceutical development of the FP manufacturing process was described in detail. Formulation studies were performed to define the optimal composition of the vaccine; it was decided to keep the same excipients as in the currently registered 2-vial Shingrix vaccine (with lyophilized gE component) in order to avoid the need for additional clinical studies. A comparability assessment was performed which showed that Shingrix liquid vaccine is comparable to the 2-vial Shingrix vaccine.

A description was also provided for the container closure system and its compatibility. The container closure of the FP is a glass syringe with a butyl rubber plunger stopper. All components comply with the respective Ph. Eur. monographs. The container components were described in detail and specifications were provided as well as information on the dimensions. Extractables and leachables studies have been performed which did not reveal any compounds of concern. As the FP is considered an integrated drug-device combination, also a notified body opinion was provided for the syringes. The syringes are deemed suitable.

The FP manufacturing process and process controls are described in detail. The FP manufacturing process was appropriately validated. Supporting validation studies were provided including validation of aseptic

filling of the vaccine and validation of sterile filtration. The gE antigen is known to be prone to methionine oxidation. The company has demonstrated the absence of potential impact on gE structure and thus immunogenicity. The company has proposed actions to further limit and monitor the methionine oxidation and has also committed to provide methionine oxidation release test results for commercial FP lots when results are available, post-approval- **recommendation 1**.

All excipients used in the FP are of compendial grade (compliant with Ph. Eur.), except QS-21 and DOPC for which in-house specifications are provided. Specifications for QS-21 and DOPC have been provided and are considered acceptable and properly justified. No excipients derived from human or animal origin are used and no novel excipients are included.

Specifications are provided for the FP. The proposed specifications are deemed suitable and are similar to the ones approved for the 2-vial Shingrix vaccine.

Descriptions are provided for the analytical methods. All methods are properly validated. Methods that are identical to the ones used for release testing of the 2-vial Shingrix vaccine have been validated previously. New methods or methods that were modified (to accommodate the different matrix of the fully liquid Shingrix vaccine) were revalidated. Batch data were provided for FP batches; all test results complied with the specifications. Also, impurities have been described. A risk assessment has been performed for possible nitrosamine contamination; the evaluation showed that the risk is negligible to non-existent.

Reference standards have been described. All reference standards were adequately documented and have been properly qualified. Adequate protocols were provided for qualification of future reference standards.

Stability studies have been performed at long term storage conditions and accelerated conditions. All results comply with the specifications.

The proposed FP shelf life of 36 months (when stored at 2-8°C) for Shingrix liquid vaccine is deemed acceptable. The applicant is, however, requested to provide the final stability data of the PPQ FP batches when the stability studies have been finalised (**recommendation 2**).

The applicant has also proposed 2 post-approval change management protocols (PACMP): one to implement an additional FP manufacturing site, and a second one to implement 'point of fill sterile filtration'. Both PACMPs provide details on the proposed changes as well as on the validation approach. Both PACMPs are deemed acceptable. The changes can be implemented via an implementing type IB Variation that contains the results of the process validation and the comparability analysis.

In conclusion, no major objections have been observed for quality. A few other concerns have been raised which were all properly addressed. Therefore, based on the review of the quality data provided, the line extension application for Shingrix liquid vaccine is deemed approvable from the quality point of view.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of GlaxoSmithKline Biologicals to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to provide the methionine oxidation release test results for a specified number of commercial lots of gE/AS01$_B$ Liquid.

2. The applicant is requested to provide the final stability data of the PPQ finished product batches when the stability studies have been finalised.

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical data presented in the original Shingrix dossier for the 2-vial gE/AS01$_B$ vaccine are considered applicable for the gE/AS01$_B$ Liquid vaccine. The original Shingrix dossier for MAA included nonclinical pharmacology and toxicology studies that were conducted with the 2-vial gE/AS01B vaccine and were complemented by nonclinical pharmacology, pharmacokinetics and toxicology studies conducted with the AS01$_B$ Adjuvant System, as well as studies conducted with the QS-21 and MPL immunoenhancer components of this Adjuvant System family. In particular, toxicology studies conducted with the 2-vial gE/AS01$_B$ vaccine, AS01$_B$ alone, MPL and QS-21 were included.

The pharmacology, pharmacokinetics and toxicology studies conducted in mice, dogs, rats and rabbits showed that the 2-vial gE/AS01$_B$ vaccine induces a strong and antigen-specific immune response and is well-tolerated in animal models. These studies also support the justification and selection of the adjuvant. Altogether, these nonclinical studies support the safe use of Shingrix in human subjects.

One nonclinical pharmacology (immunogenicity) study was conducted in mice as part of the technical bridging data to support the technical comparability between the 2-vial gE/AS01$_B$ vaccine and the gE/AS01$_B$ Liquid vaccine [Study B-000-OJ1].

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

There is no new in vitro data.

New in vivo nonclinical data was submitted to support the use of Shingrix in the fully liquid formulation:

Study B-000-OJ1: in vivo testing of B-000-OJ1: Shingrix fully liquid in female C57BL/6 mice.

Study objective

The primary objective of this study was to the evaluate bioequivalence of the anti-gE IgG titers between commercial Shingrix reconstituted vaccine (RV), Shingrix fully liquid (FL), and Shingrix FL formulation that underwent stress conditions to predicted time points to determine the effect of changes in subpopulation composition over time. This analysis was performed on samples collected 3 weeks post first vaccination (3wpl) and 3 weeks post second vaccination (3wp2). The success criteria for this study was determined by establishing the bioequivalence between each Shingrix FL formulation (including groups 3-5) and the commercial Shingrix RV (group 2) at the 3wp2 time point. Additionally,

an exploratory objective was to compare the CD4+ T-cell responses elicited by FL stress condition, non-stressed FL and commercial Shingrix.

Formulations evaluated

- 2-vial gE/AS01$_B$ vaccine

- gE/AS01$_B$ Liquid vaccine

- gE/AS01$_B$ Liquid vaccine (stressed material 1)

- gE/AS01$_B$ Liquid vaccine (stressed material 2)

The study was conducted with commercially available material for the 2-vial gE/AS01$_B$ vaccine and small-scale GMP lots for the gE/AS01$_B$ Liquid vaccine that are representative of the final vaccine formulation and manufacturing process intended for clinical use.

Choice of animal model

The C57BL/6 mouse has been selected because it is a standard rodent species and strain recognized by international regulatory agencies for use in immunogenicity studies. The majority of the immunogenicity studies included in the original Shingrix dossier for the 2-vial gE/AS01$_B$ vaccine that were conducted to evaluate vaccine potency were previously conducted in mice. Furthermore, female mice are traditionally considered more responsive in immunization studies.

Study design

Seventy-eight female C57BL/6 mice 6-8 weeks old (6 mice/group for G1, 18 mice/group for G2-5) received a 5 µg dose of gE/AS01$_B$ (commercially available, 2-vial gE/AS01$_B$ vaccine (G2), gE/AS01$_B$ Liquid vaccine (G3), gE/AS01$_B$ Liquid vaccine stressed material 1 (G4), gE/AS01$_B$ Liquid vaccine stressed material 2 (G5) or saline control (G1). Mice received 50 µL/dose by intramuscular immunization on day O (DO) and day 21 (D21). To assess vaccine-elicited immunogenicity, serum was collected on D21 and day 42 (D42) to measure anti-gE lgG response.

Results

The anti-gE humoral responses was measured by an anti-gE IgG binding ELISA. Results from both D21 and D42 demonstrate that all gE/AS01$_B$ Liquid vaccine groups (G3, G4, G5) are equivalent to commercial lyophilized Shingrix (G2).

The cellular mediated response was examined as an exploratory objective (6 mice per group). The percent of CD4+ T cell populations was determined on D42 in cells with/without expression of IFNy and/or IL2. Equivalence between the gE/AS01$_B$ Liquid groups (G3, G4, G5) and the reference group (G2) is not demonstrated for all comparisons. As gE/AS01$_B$ Liquid groups (G3, G4, G5) showed a slight increase in their geomean compared to the reference group (G2), the non-inferiority of these gE/AS01$_B$ Liquid groups over the reference is demonstrated for all comparisons except for stressed material 1 (G4) on the INFg+IL2-. As a reminder, using only 6 mice per group probably underpowers the demonstration of equivalence.

Conclusions

The primary objective of this study was to examine the effect of observed changes in gE structure in Shingrix FL formulations by determining the bioequivalence between Shingrix FL samples and the commercial lyophilized Shingrix. Results measuring the anti-gE lgG binding measured by ELISA from serum collected at D21 (3wpl) and D42 (3wp2) showed that at both timepoints all Shingrix FL lot 2.0

groups were bioequivalent to the commercial lyophilized Shingrix. These data indicate that the observed changes in gE structure does not impact the immunogenicity of the Shingrix FL samples.

The exploratory objective of this study was to compare the CD4+ T-cell responses elicited by Shingrix FL samples and commercial lyophilized Shingrix. Results showed that a bioequivalence was established for some of the groups. Non-inferiority for all Shingrix FL was demonstrated when comparing the IFNY+/IL2+, IFNY-/IL2+, and total response. For the lfNY+/IL2- response, G3 and G5 demonstrate non-inferiority. G4 did not demonstrate non-inferiority. The low sample number (6) likely underpowers the demonstration especially given the high variability associated with this assay. Overall, the response between the Shingrix FL groups and the commercial lyophilized product is consistent.

The bioequivalence in terms of CD4+ T-cell responses was not proven as the low sample number (6) and high variability associated with the assays underpowers the demonstration of bioequivalence.

Nevertheless, similar anti-gE IgG responses were observed with gE/AS01$_B$ fully liquid formulation and the 2-vial formulation. Therefore, there are no concerns with respect to the immunogenicity of gE due to the change to a fully liquid formulation.

2.5.2.2. Secondary pharmacodynamic studies

As per the original Shingrix dossier for the 2-vial gE/AS01$_B$ vaccine, no secondary pharmacodynamics studies were conducted, in accordance with current international vaccine guidelines. This is acceptable.

2.5.2.3. Safety pharmacology programme

For safety pharmacology studies supporting the gE/AS01$_B$ Liquid vaccine, reference is made to the original Shingrix dossier for the 2-vial gE/AS01$_B$ vaccine.

As the vaccine composition of the gE/AS01$_B$ Liquid vaccine is the same as the licensed 2-vial gE/AS01$_B$ vaccine post reconstitution, the nonclinical safety pharmacology data presented in the original Shingrix dossier for the 2-vial gE/AS01$_B$ vaccine are considered applicable for the gE/AS01$_B$ Liquid vaccine.

2.5.2.4. Pharmacodynamic drug interactions

As per the original Shingrix dossier for the 2-vial AS01$_B$ vaccine, no pharmacodynamics drug interaction studies were conducted, in accordance with current international vaccine guidelines.

2.5.3. Pharmacokinetics

For pharmacokinetic studies supporting the gE/AS01$_B$ Liquid vaccine, reference is made to the original Shingrix dossier for the 2-vial gE/AS01$_B$ vaccine. As the vaccine composition of the fully liquid formulation is the same as the licensed 2- vial gE/AS01$_B$ vaccine post reconstitution, the nonclinical pharmacokinetics data presented in the original Shingrix for the 2-vial gE/AS01$_B$ vaccine are considered applicable for the gE/AS01$_B$ Liquid vaccine. This is acceptable.

2.5.4. Toxicology

For toxicology studies supporting the gE/AS01$_B$ Liquid vaccine, reference is made to the original Shingrix dossier for the 2-vial gE/AS01$_B$ vaccine.

As the vaccine composition of the fully liquid formulation is the same as the licensed 2-vial gE/AS01$_B$ vaccine post reconstitution and no new impurities have been identified, the nonclinical toxicology data presented in the original Shingrix dossier for the 2-vial gE/AS01$_B$ vaccine are considered applicable for the gE/AS01$_B$ Liquid vaccine. This is acceptable.

2.5.5. Ecotoxicity/environmental risk assessment

At the time of the original marketing application for Shingrix an Environmental Risk Assessment (ERA) was not conducted, in accordance with EMA Guidance (CHMP 2006) which stated that vaccines were exempt due to the nature of their constituents. A new pharmaceutical form is introduced (fully liquid formulation) which will be a substitution of the powder and the suspension for reconstitution in the same patient population. An increase in environmental exposure is not expected due to this new formulation. In accordance with the current EMA Guidance (CHMP, 2024), the justification to not conduct ERA studies for Shingrix remained due to the physio-chemical nature of its constituents and vaccines without adjuvants are unlikely to result in a risk to the environment.

2.5.6. Discussion on non-clinical aspects

The nonclinical data presented in the original Shingrix dossier for the 2-vial gE/AS01$_B$ vaccine are considered applicable for the gE/AS01$_B$ Liquid vaccine. The original Shingrix dossier for MAA includes nonclinical pharmacology and toxicology studies that were conducted with the 2-vial gE/AS01$_B$ vaccine and were complemented by nonclinical pharmacology, pharmacokinetics and toxicology studies conducted with the AS01$_B$ Adjuvant System, as well as studies conducted with the QS-21 and MPL immunoenhancer components of this Adjuvant System family. In particular, toxicology studies conducted with the 2-vial gE/AS01$_B$ vaccine, AS01$_B$ alone, MPL and QS-21 were included.

The pharmacology, pharmacokinetics and toxicology studies conducted in mice, dogs, rats and rabbits showed that the 2-vial gE/AS01$_B$ vaccine induces a strong and antigen-specific immune response and is well-tolerated in animal models. These studies also support the justification and selection of the adjuvant. Altogether, these nonclinical studies support the safe use of Shingrix in human subjects.

One nonclinical pharmacology (immunogenicity) study was conducted in mice as part of the technical bridging data to support the technical comparability between the 2-vial gE/AS01$_B$ vaccine and the gE/AS01$_B$ Liquid vaccine [Study B-000-OJ1].

Study B-000-OJ1 demonstrates bioequivalence between the two vaccine presentations in terms of anti-gE IgG responses.

The active substance and the components of the adjuvating system are natural substances, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, the gE/AS01$_B$ Liquid vaccine is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Study B-000-OJ1 demonstrates bioequivalence between the two vaccine presentations in terms of anti-gE IgG responses.

The active substance and the components of the adjuvating system are natural substances, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, the gE/AS01$_B$ Liquid vaccine is not expected to pose a risk to the environment. The line extension is approvable from a nonclinical point of view.

2.6. Clinical aspects

No new efficacy, immunogenicity and safety clinical data were submitted in support of this Application. The MAH considered the existing clinical package supporting the currently approved pharmaceutical form of Shingrix (gE/AS01$_B$) as adequate and sufficient to also support the new liquid form of the vaccine (gE/AS01$_B$ Liquid vaccine). The absence of submission of additional clinical data was previously

agreed by CHMP (EMA/SA/0000079850 and EMA/SA/0000173718), provided comparability is demonstrated at quality level between the current registered lyophilized presentation (gE/AS01$_B$) and the newly proposed liquid formulation (gE/AS01$_B$ Liquid). It is considered that this demonstration would be sufficiently predictive to ensure no adverse impact on safety and/or efficacy (immunogenicity) of the product.

Comparability of the gE/AS01$_B$ Liquid vaccine with the currently approved gE/AS01$_B$ vaccine (lyophilized presentation) has been appropriately demonstrated based on analytical tools. Consequently, the absence of additional clinical data to support the approval of the gE/AS01$_B$ Liquid vaccine is acknowledged and agreed.

2.7. Risk Management Plan

The updated RMP version 10.0 that was submitted during this procedure has been consolidated with the RMP version 12.2 approved on 02 October 2025 (procedure EMA/VR/0000263592).

The consolidated RMP, version 12.3, has been submitted and agreed as final for this procedure.

2.7.1. Safety concerns

Table SVIII.1: Summary of safety concerns in the consolidated RMP version 12.3:

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

Having considered the data in the safety specification

It is agreed that the safety concerns listed by the MAH are appropriate.

2.7.2. Pharmacovigilance plan

No new efficacy, immunogenicity and safety clinical data were submitted in support of this Application.

The changes to the RMP (version 10.0) are administrative and editorial only.

Consequently, there were no changes to PART III: Pharmacovigilance plan (Including Post Authorisation Studies) in RMP version 10.0 compared to RMP version 7.0 (DLP 12 Oct 2020), on which version 10 was based.

However, the MAH took the opportunity to create RMP version 12.3 by consolidating version 10.0 with RMP version 12.2, which was approved on 02 October 2025 (procedure EMA/VR/0000263592).

All relevant sections and annexes of the RMP have been updated accordingly.

2.7.3. Risk minimisation measures

No new efficacy, immunogenicity and safety clinical data were submitted in support of this Application.

The changes to the RMP (version 10.0) were administrative and editorial only.

There were no changes to PART V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities) in RMP version 10.0 compared to RMP version 7.0 (DLP 12 Oct 2020), on which version 10.0 was based.

However, the MAH took the opportunity to create RMP version 12.3 by consolidating version 10.0 with RMP version 12.2, which was approved on 02 October 2025 (procedure EMA/VR/0000263592).

All relevant sections and annexes of the RMP have been updated accordingly.

2.7.4. Conclusion

The CHMP considered that the Risk Management Plan version 12.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by GlaxoSmithKline Biologicals fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by GlaxoSmithKline Biologicals and has been found acceptable for the following reasons:

The main changes in the PL are the title and section 6. An additional change is the section 6.6 *special precautions for disposal and other handling* of the SmPC. The instructions for the pre-filled syringe are intended for HCP only. The proposed differences in the PL are minimal and do not concern safety information critical for the patient. There is no change proposed to any safety information, indication, dosage and administration or composition. Thus, it was previously agreed by EMA that the User Testing or any form of bridging are not necessary in terms of content. The justification of the MAH for not providing a user testing report is deemed acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

• adults 50 years of age or older;

• adults 18 years of age or older at increased risk of HZ.

The currently approved pharmaceutical form, referred to as 2-vial gE/AS01$_B$, is supplied as a single-dose vial of the lyophilized glycoprotein E (gE) antigen component (50 µg) to be reconstituted with the accompanying vial of the AS01$_B$ adjuvant suspension component (50 µg MPL, 50 µg QS-21).

The MAH has developed a fully liquid suspension for injection (gE/AS01$_B$ Liquid) of the Shingrix vaccine, resulting from the co-formulation of the Shingrix gE antigen (no longer lyophilised) and adjuvant components, with the same composition as the current 2-vial gE/AS01$_B$ vaccine. The gE/AS01$_B$ Liquid presentation is a single container pre-filled syringe. gE/AS01$_B$ Liquid is indicated for the same adult population as currently approved for 2-vial gE/AS01$_B$.

3.1.2. Available therapies and unmet medical need

Treatment

The primary treatment for HZ involves antiviral medications, such as acyclovir, valacyclovir, or famciclovir. These medications can help to reduce the severity and duration of the illness, as well as reduce the risk of complications. Antiviral medications are most effective if started within 72 hours of the rash appearing.

Other treatments include pain relievers like ibuprofen or acetaminophen. In some cases, stronger pain medications, such as opioids or nerve pain medications, may be prescribed.

Prophylaxis

A live-attenuated VZV vaccine (Zostavax) was authorised in 2006 in the EU for use in immunocompetent adults ⩾50 YOA to prevent HZ and PHN. This vaccine was contraindicated in immunosuppressed or immunodeficient individuals due to concerns of possible vaccine-associated disseminated disease. On 1 June 2025, the European Commission withdrew the marketing authorisation for Zostavax (shingles (herpes zoster) vaccine (live)) in the European Union (EU). The withdrawal was at the request of the marketing authorisation holder, Merck Sharp & Dohme B.V., which notified the European Commission of its decision to permanently discontinue the marketing of the product for commercial reasons.

Shingrix is indicated for prevention of HZ and PHN, in (i) adults 50 years of age or older and (ii) adults 18 years of age or older at increased risk of HZ. The only contraindication of Shingrix is hypersensitivity to the active substances or to any of the excipients of the vaccine.

Unmet medical need

Shingrix was developed to address the medical need to prevent HZ and HZ-related complications such as PHN in older adults ⩾50 YOA and in IC adults ⩾18 YOA.

Epidemiological evidence indicates that adults ⩾ 50 YOA are at increased risk of HZ, as well as adults ⩾18 YOA with underlying medical conditions or treatments predisposing them to HZ. This includes

patients chronically using immunosuppressive medications (e.g., oncology patients and transplant recipients), patients with autoimmune diseases or other relevant chronic conditions (e.g., rheumatoid arthritis, IBD, COPD, cardiovascular diseases, renal disease, systemic lupus erythematosus, asthma, Type 2 diabetes mellitus, HIV), as well as subjects with congenital immunodeficiencies. This wide spectrum of IC/conditions altering the immune status in adults illustrates the medical need for prevention through vaccination.

3.1.3. Main clinical studies

No new clinical data were submitted in support of this Application.

The submission for this line extension was based on demonstration of technical comparability (supported by nonclinical data), without clinical data. The MAH considers the existing clinical package supporting the current approved pharmaceutical form of Shingrix as adequate to also support the new liquid form of the vaccine (gE/AS01$_B$ Liquid vaccine).

It is anticipated that the benefit-risk profile of the gE/AS01$_B$ Liquid vaccine is comparable to the benefit-risk profile of the currently approved lyophilised presentation (gE/AS01$_B$) provided demonstration of the comparability at quality level of the currently approved gE/AS01$_B$ vaccine with the gE/AS01$_B$ Liquid vaccine.

3.2. Benefit-risk assessment and discussion

Comparability of the gE/AS01$_B$ Liquid vaccine with the currently approved pharmaceutical form 2-vial gE/AS01$_B$ vaccine (lyophilized presentation) has been appropriately demonstrated based on analytical tools. Therefore, no change in terms of safety, efficacy/immunogenicity of the gE/AS01$_B$ Liquid vaccine formulation as compared to the currently approved lyophilised presentation (gE/AS01$_B$) is expected. The benefit-risk profile of the gE/AS01$_B$ Liquid vaccine is anticipated to be comparable to the benefit risk profile of Shingrix lyophilised presentation.

Based on the above, it is considered that the high vaccine efficacy outweighs the unfavourable effects linked mainly to reactogenicity as no important risks were otherwise identified.

3.3. Conclusions

The overall benefit/risk balance of Shingrix is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and nonclinical, the CHMP considers by consensus that the benefit-risk balance of, Shingrix suspension for injection is favourable in the following indication(s):

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

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

The use of Shingrix should be in accordance with official recommendations.

The CHMP therefore recommends the extension of the marketing authorisation for Shingrix subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Official batch release

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

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.