Date: 4 March 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Shingrix

International non-proprietary name: Varicella zoster virus glycoprotein E antigen

Pharmaceutical form: powder and suspension for suspension for injection

Dosage strength: 50 µg

Route(s) of administration: i.m.

Marketing Authorisation Holder: GlaxoSmithKline AG

Marketing Authorisation No.: 67987

Decision and Decision date: approved on 7 October 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse Event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
gE	glycoprotein E
GLP	Good Laboratory Practice
GMC	Geometric Mean Concentration
HCT	Haematopoietic stem Cell Transplant
HZ	Herpes Zoster
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
mTVC	Modified Total Vaccinated Cohort
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PHN	Post-herpetic neuralgia
pIMD	Potential Immune-Mediated Disease
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
Tdap	Tetanus, diphtheria, pertussis
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
TVC	Total Vaccinated Cohort
VE	Vaccine Efficacy
VRR	Vaccine Response Rate
VZV	Varicella zoster virus
YOA	Years of Age

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance Varicella zoster virus glycoprotein E antigen of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Shingrix is indicated for prevention of herpes zoster in adults aged 50 years or older and in adults aged 18 years or older with increased risk for HZ.
The use of Shingrix should be in accordance with official vaccination recommendations.

2.2.2 Approved Indication

Shingrix is indicated for the prevention of herpes zoster (HZ) in adults aged 50 years or older and in adults aged 18 years or older at increased risk of HZ.
See "Warnings and Precautions" and "Properties/Effects".
The use of Shingrix should be based on official vaccination recommendations.

2.2.3 Requested Dosage

The primary vaccination schedule consists of two doses of 0.5 ml each: an initial dose followed by a second dose 2-6 months later. In people, who are immunocompromised or immunosuppressed due to disease or therapy and who would benefit from a shorter vaccination schedule, the second dose may be administered 1 to 2 months after the first dose.
The need for booster doses following the primary vaccination schedule has not been established.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	29 April 2020
Formal control completed	20 May 2020
List of Questions (LoQ)	24 September 2020
Answers to LoQ	20 December 2020
Predecision	30 March 2021
Answers to Predecision	25 May 2021
Labelling corrections	16 August 2021
Answers to Labelling corrections:	8 September 2021
Final Decision	7 October 2021
Decision	approval

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3 Medical Context

Shingles (or herpes zoster [HZ]) is the result of the reactivation of varicella zoster virus (VZV), which causes varicella (chickenpox) as primary infection. It is estimated that about 20% of people who have had chickenpox, will get a herpes zoster infection at least once later in life. HZ affects about 20-25% of the ageing population in Switzerland. It is characterised by a painful, unilateral vesicular rash. This usually occurs in a restricted dermatomal distribution corresponding to the sensory fields of the latently infected ganglia.

Reactivation of the virus is more common in the elderly or in older people with a weakened immune system. Healthy people between 50-60 years of age mostly have mild HZ courses without post-herpetic neuralgia (PHN), while older people ≥75 years of age often have more severe symptoms and more often require hospitalisation due to HZ infection. Patients with different forms of immunosuppression can have severe, sometimes life-threatening courses at younger ages. The severity of HZ and its complications also increases in those over 50 years of age who have had shingles at least once in their lifetime. Chronic pain can occur weeks or months after shingles. In 20% of patients over 65 years of age, this condition lasts for more than three months (PHN). Other complications include ocular and neurological complications, and bacterial superinfection of the skin. In Switzerland, more than 20,000 consultations per year are related to shingles, half of which involve people over the age of 65. (Epidemiology, clinical manifestations, and diagnosis of herpes zoster, UpToDate; https://www.bag.admin.ch/bag/de/home/krankheiten/krankheiten-im-ueberblick/windpocken.html; Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI) p.21).

The only currently available HZ vaccine in Switzerland is a live-attenuated vaccine, which is contraindicated in different forms of immunosuppression.

There are currently no established immune correlates of protection against HZ and PHN.

4 Quality Aspects

4.1 Drug Substance

Varicella zoster virus (VZV) glycoprotein E (gE) is the most abundant virion envelope glycoprotein and the predominant VZV glycoprotein expressed on the surface of virus-infected cells.

The drug substance, recombinant VZV gE, is produced from a mammalian cell line (Chinese Hamster Ovary, CHO) using amplification steps, followed by an antigen production step. At the end of the production step, the cell suspension constitutes the gE single harvest. It is then clarified by depth filtration, filtered and stored before purification. The clarified harvest is further processed by several purification and virus inactivation steps including different types of chromatography, a low pH treatment step for viral inactivation, an ultrafiltration step, nanofiltration and post-purification filtration for bioburden control before freezing and storage at -45°C.

The characterisation of the physicochemical and biological properties of the drug substance and its impurities were performed using state-of-the-art methods.

The specifications for release include relevant tests and acceptance criteria, e.g. for description, pH, identity, purity, antigenic activity, protein, endotoxin and host-cell protein contents. Specifications are based on clinical experience, batch analysis data (release and stability data) and are in conformance with current compendial or regulatory guidelines. All analytical methods are described, and non-compendial methods have been validated in accordance with ICH guidelines.

Batch analysis data for non-clinical batches, clinical batches and process validation batches were provided. Comparable quality was shown throughout the clinical development. Comparability between

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three commercial-consistency gE Purified Bulk (PPQ) batches and reference gE Purified Bulk batches (Phase III clinical batches and technical development batches) was demonstrated.

The drug substance is stored at -45°C. No significant changes were observed under the proposed storage conditions. A shelf life of 60 months has been accepted.

4.2 Drug Product

The finished product consists of a lyophilised powder vial (drug product) and an adjuvant vial ($AS01_B$ adjuvants) used to reconstitute the vaccine, in order to obtain a liquid mono-dose preparation for intramuscular injection. The volume per nominal dose is 0.5 ml.

The drug product vial contains a lyophilised powder of 50 µg VZV glycoprotein E antigen with the following excipients: sucrose; polysorbate 80; sodium dihydrogen phosphate dihydrate; dipotassium phosphate. All these excipients are compliant with Ph. Eur. standards.

The $AS01_B$ adjuvant vial contains a suspension for injection with the following excipients: QS-21 (a triterpene glycoside purified from the bark of the tree Quillaja saponaria Molina), MPL (3-Odesacyl-4'-monophosphoryl lipid A), dioleoyl phosphatidylcholine (DOPC); cholesterol; sodium chloride; disodium phosphate anhydrous; potassium dihydrogen phosphate; water for injections. With the exception of QS-21 and DOPC, the excipients are compliant with Ph. Eur. standards. The target fill volume includes an overfill that ensures a nominal injection volume of 0.5 ml.

The manufacturing process for the drug product consists of formulation, sterile filtration, aseptic filling, lyophilisation and visual inspection steps. Process validation studies were executed at commercial scale using three validation batches.

The specifications for the drug product were set based on compendial requirements, experience from clinical trials and commercial process capability. They include relevant tests and limits, e.g. for description, pH, osmolality, identity, protein content, bacterial endotoxin content, water content, polysorbate 80 content, sucrose content, potency and sterility. All non-compendial methods are validated in accordance with ICH guidelines.

Batch analysis data for three commercial consistency lots have been provided. All batch release data comply with the commercial drug product specifications.

The manufacturing process for the $AS01_B$ adjuvants consists of formulation, sterile filtration, filling and visual inspection steps. Process validation studies were executed at commercial scale using three validation batches.

The specifications for the $AS01_B$ adjuvants were set based on compendial requirements, experience from clinical trials and commercial process capability. They include relevant tests and limits, e.g. for description, pH, osmolality, sterility, volume, contents of MPL, QS-21, DOPC, and cholesterol, limit tests for QS-21-H, lyso-DOPC and polydispersity, as well as MPL congener distribution. All non-compendial methods are validated in accordance with ICH guidelines.

Batch analysis data for nine commercial-consistency lots have been provided. All batch release data comply with the commercial drug product specifications.

The primary container closure system for the drug product and the $AS01_B$ adjuvants consists of a colourless 3 mL type I glass vial. The drug product vial is closed with a bromobutyl type I rubber stopper for the lyophilised formulation, and the $AS01_B$ adjuvant vial is closed with a chlorobutyl type I rubber stopper. Both the drug product and the $AS01_B$ adjuvant vials are finally sealed with an

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aluminium flip-off cap. All components coming into contact with the finished product comply with Ph. Eur. requirements.

The drug product and the $AS01_B$ adjuvants are stored at 2-8°C (no freezing and protected from light). No significant changes were observed under the proposed storage conditions. A shelf life of 36 months has been accepted. As the finished product consists of two separate vials (drug product and $AS01_B$ adjuvants), the expiry date of the dual presentation will be determined by whichever component expires earliest. The drug product and $AS01_B$ adjuvant system may sustain exposure to a temperature excursion for up to 14 days at 25°C during the 36-month shelf life.
To avoid potential contamination and to preserve the sterility of the final reconstituted vaccine, the vaccine must be used promptly after reconstitution. If this is not possible, the reconstituted vaccine should be stored in a refrigerator (2-8°C) and used within a maximum of 6 hours.

4.3 Quality Conclusions

The manufacturing processes (drug substance, drug product and $AS01_B$ adjuvants) are well described and demonstrate a consistent quality. The shelf lives of drug substance, drug product and $AS01_B$ adjuvants are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk for adventitious agents is minimised.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Shingrix, the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the EMA assessment reports dated 25 January 2018 und 23 July 2020 and provided by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Shingrix in the proposed indication. The pharmaco-toxicological profiles of the vaccine and the adjuvant system have been sufficiently characterised. No safety issues were identified in the nonclinical studies that would be of concern for human use. The safety margins are considered to be sufficient. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals and in the risk management plan.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The evaluation of the clinical pharmacology data in this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment reports and respective product information texts from the EMA and FDA were used as a basis for the clinical pharmacology evaluation.

Interactions

Additional studies evaluating the effect of co-administration of Shingrix with a pneumococcal vaccine and tetanus, diphtheria, pertussis (Tdap) vaccine were submitted.

In a randomised, open-label, multicentre study, the interaction between Pneumovax-23 and Shingrix in healthy elderly subjects ≥50 years of age without any immunosuppressive condition or therapy was evaluated. Only 12 serotypes included in Pneumovax 23 were examined. No significant interference was observed between the HZ/su and Pneumovax 23 vaccines when co-administered compared to when given separately in terms of immunogenicity results. Solicited adverse events were more frequent with the combination.

The interaction between Tdap (Boostrix) and Shingrix was examined in a phase III, 1:1 randomised open-label multicentre study in healthy elderly subjects >50 years of age without any immunosuppressive condition or therapy (13 centres in the USA). Not all co-primary objectives of the study were met. The two types of immune response to Shingrix (vaccine response rate [VRR] and geometric mean concentration [GMC] ratios) when co-administered with Boostrix were regarded as non-inferior compared to when the vaccines were given separately. However, Shingrix influenced the humoral immune response to Boostrix, as non-inferiority of co-administered Boostrix and Shingrix compared to Boostrix separately was not demonstrated for all antigens. The adjusted GMC ratio for anti-PRN antibodies (Control group over Co-Ad group) was not <1.5. Shingrix did not influence the anti-D, anti-T, anti-FHA and anti-PT responses to Boostrix. A slightly higher rate of solicited adverse events was seen in the co-administration group.

6.2 Dose Finding and Dose Recommendation

The evaluation of the clinical data in this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment reports and respective product information texts from the EMA and FDA were used as a basis for the clinical evaluation.

6.3 Efficacy

The evaluation of the clinical efficacy and safety data in this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment reports and respective product information texts from the EMA and FDA were used as a basis for the evaluation. The assessment focused on the efficacy of Shingrix in subjects 18 years and older at increased risk of HZ.

Efficacy in this population is based on study ZOSTER-002. This was a phase III, 1:1 randomised, observer-blind, placebo-controlled, multicentre study in adults with autologous haematopoietic stem cell transplant (HCT) recipients in 28 countries. Study Zoster-002 assessed the prophylactic efficacy, safety and immunogenicity of two doses of Shingrix (first dose 0, second dose 1-2 months later). Study end was planned when at least 125 confirmed HZ cases were found. All subjects were to be followed at least until they completed Visit 4 (i.e. until Month 13), approximately 12 months after the second dose. The exact study duration varied between subjects. The median follow-up time was approximately 21 months, approximately 22 months in the Shingrix group and approximately 20 months in the placebo group.

The primary endpoint was vaccine efficacy (VE) in the prevention of HZ compared to placebo in adults with autologous haematopoietic stem cell transplant in the modified total vaccinated cohort (mTVC).

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Secondary endpoints included duration of 'worst' HZ-associated pain, confirmed HZ-associated complications, PHN, anti-gE Ab concentrations as determined by ELISA in a sub-cohort of subjects at various timepoints, solicited and unsolicited AEs, fatal and serious AEs, potential immune-mediated disease (pIMD) and occurrence of relapse (underlying malignancy/disease). Except for the analyses of the primary endpoint, all other analyses were exploratory as these were not controlled for a type I error.

Compared to other Shingrix studies Zoster-002 had a lower completion rate: 75.3% of subjects in the Shingrix group and 72.7% in the placebo group completed the study. A substantial number of patients were withdrawn because of serious AEs (13.2% overall). 111 subjects did not receive the second vaccination and were excluded from the mTVC: 49 subjects in the Shingrix group and 62 subjects in the placebo group.

The primary objective of the study was met, with an overall HZ VE (first or only episode of HZ) of 68.17% (95% CI: 55.56% - 77.53%). The efficacy was, however, lower compared to elderly subjects without any immunocompromised condition, although the follow-up period was shorter compared to studies with elderly subjects. Analysis of the total vaccinated cohort (TVC) showed lower percentages: 63.71% (95% CI: 51.82% -72.92%).

In study Zoster-002 an age-stratified analysis showed a small advantage in subjects 18-49 years of age (YOA): 71.77% (95% CI: 38.75% - 88.25%) compared to subjects ≥50 YOA: 67.34% (95% CI: 52.60% - 77.89%). Female patients showed better efficacy compared to male patients. Interestingly, patients with multiple myeloma had better efficacy compared to other diagnoses. The period of antiviral prophylaxis also showed some effect. Higher efficacy was seen in patients with longer antiviral prophylaxis (> 3-6 months) compared to 0-3 months of antiviral prophylaxis.

Further studies investigated the anti-glycoprotein E (anti-gE) antibody response to Shingrix in adults with haematological malignancies, HIV, solid tumours and receiving chemotherapy or a renal transplant who are on chronic treatment with immunosuppressants. As there is no known immune correlate of protection, no conclusions on efficacy can be based on these results. However, these data indicated a response to vaccination and can therefore be considered supportive for the use of Shingrix in immunocompromised patients.

Data indicate that vaccine efficacy decreased slightly 5 to 7 years following vaccination. This decrease was somewhat more pronounced in the older age groups. A similar pattern was seen for the immunogenicity data, with decreasing frequency of gE-specific CD4(2+) T-cells and anti-gE antibody concentrations. As there is no known immune correlate of protection, the clinical relevance of this is unclear. It can be accepted that the long-term protection of Shingrix is not fully known beyond 4-5 years post-vaccination, and that data on long-term efficacy will become available post-marketing. The need for a booster dose has not been evaluated.

Subjects with a prior HZ infection were excluded from the studies in healthy elderly subjects ≥50 YOA. Based on the results of a small exploratory study in subjects with previous HZ infections, a potential risk for increased HZ recurrence in this population cannot be ruled out. A warning to the effect that only limited data are available to support efficacy in this population is included in the information for healthcare professionals, and further data will become available post-marketing.

6.4 Safety

A total of 1,587 subjects with immunocompromising conditions received at least one dose of Shingrix in the submitted studies. In these studies, the compliance with the two-dose schedule was high, ranging from 83.9% to 95.5% in the Shingrix groups. A total of 443 subjects 18-49 YOA and 1,144 subjects ≥50 YOA received at least one dose of Shingrix.

ZOSTER-002

As expected, more local and systemic reactogenicity was observed with Shingrix compared to placebo. There were no apparent differences in the 30-day period for unsolicited AEs. There were no apparent differences between the Shingrix and placebo groups in the percentages of subjects with SAEs, SAEs reported with a causal relationship to vaccination as per investigator assessment or fatal SAEs. No fatal SAEs with a causal relationship to vaccination (as per investigator assessment) were

reported in the study. The distribution of subjects with pIMDs was 13:8. The distribution of subjects with drug-related pIMDs was 4:0. However, there was no cluster in the nature of the pIMDs reported, and no clear safety concern was identified. No apparent differences between the Shingrix and placebo groups in the percentages of subjects with relapse or disease progression were reported during the study.

No clear safety signals were identified in adults ≥18 YOA with haematological malignancies (ZOSTER-039), apart from markedly higher local and systemic reactogenicity. The percentages of subjects with progression of the haematological malignancy or relapse of the haematological malignancy was not higher in the Shingrix groups than in the placebo group.

Overall, there were no prohibitive safety signals in adults ≥18 YOA with solid tumours receiving chemotherapy (ZOSTER-028). Local and systemic reactogenicity was higher in the Shingrix group compared to placebo. Unsolicited AEs were more or less equally distributed. Numbers and percentages of subjects with SAEs and (S)AEs leading to study withdrawal reported during the study were generally well balanced between the Shingrix and placebo groups. During the study, no subjects were reported with SAEs with a causal relationship to vaccination as per investigator assessment.

In adults ≥18 YOA with stable renal transplants on chronic immunosuppressants (ZOSTER-041), higher local reactogenicity was observed in the Shingrix group compared to the placebo group. Regarding systemic reactogenicity, headache, myalgia, fever and shivering were more frequent after Shingrix. Drug-related unsolicited AEs were somewhat more frequent in the Shingrix group. Numbers and percentages of subjects with SAEs (including fatalities) and (S)AEs leading to study withdrawal reported during the study were generally balanced between Shingrix and placebo group. No SAEs were considered causally related to vaccination as assessed by the investigator.

From first vaccination up to study end, the number (%) of subjects with fatal SAEs was one (0.8%) in the Shingrix (onset at 17-days post-dose 2) and one (0.8%) in the placebo group (onset at 229 days post-dose 2). The Shingrix recipient died of purulent meningitis at 43 days post-dose 2, whereas the placebo recipient died of coronary artery disease complicated by vein graft thrombosis and myocardial infarction at 229 days post-dose 2; neither was considered causally related to vaccination as assessed by the investigator.

From 30 days post last vaccination up to study end and from first vaccination up to study end, 3.0% of Shingrix recipients reported at least one pIMD event (two with gout, one with type I diabetes mellitus and one with IgA nephropathy), while 1.5% of placebo recipients reported at least one pIMD event (two with IgA nephropathies); none were considered causally related to vaccination as assessed by the investigator.

There was no clustering of biopsy-proven renal allograft rejection or malfunction of renal allograft. From first vaccination up to study end, slightly fewer subjects in the Shingrix group had renal biopsies positive for allograft rejection. For the study duration, 20 (15.27%) Shingrix recipients and 26 (19.7%) placebo recipients had a ≥1.20-fold increase in serum creatinine compared to their pre-vaccination levels. Four, three and two Shingrix recipients and four, two and one placebo recipients had ≥1.5-, 1.75- and 2-fold increases, respectively, in serum creatinine compared to their pre-vaccination levels. The one Shingrix recipient with a ≥2.0-fold increase also had a renal biopsy positive for allograft rejection.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Shingles (or herpes zoster [HZ]) is the result of the reactivation of varicella zoster virus (VZV), and is characterised by a painful, unilateral vesicular rash. HZ affects about 20-25% of the ageing population in Switzerland. Healthy people between 50-60 years of age mostly have mild HZ courses, while older people ≥75 years of age often have more severe symptoms and more often require hospitalisation due to HZ infection. Immunocompromised individuals can have severe, sometimes life-threatening, courses at younger ages. So far, only a live-attenuated vaccine HZ vaccine that is contraindicated in different forms of immunosuppression has been available in Switzerland.

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BENEFICIAL EFFECTS

Dose-finding in healthy elderly subjects ≥50 YOA without any immunosuppressive condition or therapy is acceptable. The results of Zoster-026 supported the possibility of flexibility in the timing of the second dose (2-6 months following the first dose), although clinical experience is limited.

High efficacy and superiority over placebo were demonstrated in the following populations:

Healthy elderly subjects ≥50 YOA without any immunosuppressive condition or therapy (Study Zoster-006)

A total of 216 subjects reported a confirmed HZ episode, six in the Shingrix group and 210 in the placebo group over a mean (SD) follow-up time of 3.1 (0.5) years. The overall HZ VE was 97.16% (95% CI: 93.72% - 98.97%) and was consistent across the age strata 50-59 YOA, 60-69 YOA, and ≥70 YOA.

Healthy elderly subjects ≥70 YOA without any immunosuppressive condition or therapy (Study Zoster-022)

A total of 246 subjects reported a confirmed HZ episode, 23 in the Shingrix group and 223 in the placebo group over a median follow-up time of 3.9 years. The overall HZ VE was 89.79% (95% CI: 84.29% - 93.66%) and was consistent across the age strata of 70-79 YOA and ≥80 YOA.

Efficacy results were confirmed in a pooled analysis based on data from both studies, Zoster-006 and Zoster-022. The co-primary confirmatory objective of the pooled Zoster-006/022 studies regarding PHN VE in subjects ≥70 YOA was also met; the overall PHN VE (first or only PHN episode) was 88.78% (95% CI: 68.70% -97.10%). This was slightly higher for the 70-79 YOA stratum.

Immunocompromised patients ≥18 YOA (Study Zoster-002 – adults ≥18 YOA shortly after autologous HCT)

The phase III, 1:1 randomized, observer-blind, placebo controlled, multicentre study Zoster-002 in 28 countries evaluated the prophylactic efficacy, safety, and immunogenicity of two-dose Shingrix (first dose 0, second dose 1-2 months later) in adults receiving an autologous haematopoietic stem cell transplant (HCT). The primary endpoint was VE in the prevention of HZ compared to placebo in the mTVC population.

Efficacy in this study was lower compared to that observed in the studies with elderly subjects without any immunocompromised condition, although the follow-up time was shorter. However, superiority over placebo was shown for the primary endpoint. The overall HZ VE (first or only episode of HZ) in mTVC was 68.17% (95% CI: 55.56% - 77.53%) over a median follow-up time of approximately 21 months. Analysis of the total vaccinated cohort (TVC) showed slightly lower results: 63.71% (95% CI: 51.82% -72.92%).

UNCERTAINTIES CONCERNING THE BENEFICIAL EFFECTS

VE against PHN in confirmed HZ cases could not be demonstrated: in subjects ≥ 50 YOA with confirmed HZ, PHN was reported in 4 out of 32 subjects (12.5%) in the Shingrix group and in 46 out of 477 subjects (9.6%) in the placebo group. The overall results for VE against PHN may thus mainly be explained by high protection against HZ and the consequent prevention of PHN cases. An effect on the prevention of PHN in addition to the effect through prevention of HZ cases could not be reliably concluded.

Efficacy can only be reliably concluded for HCT patients for 22 months, leaving uncertainty about the efficacy in other immunocompromised populations and other individuals at high risk of HZ. Immunogenicity data from studies conducted in other immunosuppressed patients (patients with solid tumours; renal transplant patients) cannot be considered a surrogate of vaccine efficacy. These data can, however, be considered indicative of a response to vaccination (although no inferences can be made on the magnitude of this effect and its relevance for clinical efficacy) and, as such, supportive for the use of Shingrix in immunocompromised patients.

There remains uncertainty concerning the duration of protection and the need for a booster vaccination in all claimed target populations. This is especially relevant for individuals at high risk of HZ infection who are vaccinated early in life (<50 years of age). Further information will become available from the ongoing study Zoster-049.

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UNFAVOURABLE EFFECTS (RISKS)

No prohibitive safety signals were observed. Also in immunocompromised patients (autologous HCT, haematological malignancies, HIV, with solid tumours receiving chemotherapy, adults ≥18 YOA with stable renal transplants on chronic immunosuppressants), there were no prohibitive signals, including no proven progression of the underlying disease, proven relapse of the malignancy, proven allograft rejection or proven allograft dysfunction.

Overall, the safety profile of Shingrix is considered acceptable, and the most notable findings were:

- Marked higher local and systemic reactogenicity and somewhat more unsolicited adverse events.
- Higher local and systemic reactogenicity when given together with other vaccines: QIV Fluarix Tetra®, Pneumovax-23®, Tdap Boostrix®.
- Gout

UNCERTAINTIES CONCERNING THE UNFAVOURABLE EFFECTS

Based on the available (post-marketing) data, a risk of decreased protection in individuals with prior HZ episode(s) or VZ virus reactivation following vaccination cannot be ruled out. This will be monitored via the RMP and ongoing studies (Zoster-062).

Whether gout is a true adverse effect or a chance finding will be seen in post marketing surveillance.

BENEFIT-RISK ASSESSMENT

Healthy elderly subjects ≥50 YOA and ≥70 YOA without any immunosuppressive condition or therapy

High vaccine efficacy was seen in this population. As a result of prevention of HZ cases, an effect on the prevention of sequelae of PHN and other HZ-related complications was also seen, although this was not consistent in all age groups. An effect on the prevention of PHN and other HZ-related complications in addition to the effect through prevention of HZ cases could not be reliably concluded.

The observed higher local and systemic reactogenicity and somewhat more frequent unsolicited AEs are acceptable, given that HZ can be a painful disease.

Immunocompromised patients ≥18 YOA

Acceptable vaccine efficacy was demonstrated in adults ≥18 YOA shortly after autologous HCT, although efficacy was lower compared to healthy ≥50 YOA without previous HZ. Lower efficacy can be expected due to the severely immunocompromised status of this population. No specific safety issues were identified.

It is uncertain whether a real protection exists against HZ in immunocompromised patients outside of patients with autologous HCT studied in Zoster-002 and other individuals at high risk of HZ. Immunogenicity data from studies conducted in other immunosuppressed populations indicate that an immune response is elicited in these subgroups. However, immunogenicity data cannot be considered a surrogate of vaccine efficacy, and no inferences can be made on the magnitude of this effect and its relevance for clinical efficacy. Based on the totality of the data, i.e. efficacy in HCT patients, supportive efficacy data in patients with haematological malignancies, immune response in other immunocompromised patients and high efficacy in immunocompetent individuals, a protective effect of Shingrix in adults ≥18 years old at risk of HZ can be assumed. Given that there is currently no alternative available for this population, the uncertainty about the magnitude and duration of efficacy can be accepted.

Overall, the benefit/risk for Shingrix for the prevention of HZ in adults ≥50 years old, and adults ≥18 years old at risk of HZ is, therefore, considered positive.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Shingrix, powder and suspension for suspension for injection, was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Shingrix

Herpes zoster vaccine (recombinant, adjuvanted)

Composition

Active substances

Varicella Zoster Virus glycoprotein E (gE antigen)

Excipients

Powder (gE antigen): sucrose, polysorbate 80, sodium dihydrogen phosphate dihydrate, dipotassium phosphate
Suspension (*$AS01_B$ adjuvant):* 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL), purified *Quillaja* saponin (QS-21), dioleoyl phosphatidylcholine (DOPC), cholesterol, sodium chloride, disodium phosphate anhydrous, potassium dihydrogen phosphate, water for injections.
After reconstitution, one vaccine dose contains 1.77 mg sodium and 0.18 mg potassium.

Pharmaceutical form and active substance quantity per unit

Powder and suspension for suspension for injection.
After reconstitution, one dose (0.5 ml) contains 50 micrograms of gE antigen[1] adjuvanted with $AS01_B$[2].
[1] Varicella Zoster Virus (VZV) glycoprotein E (gE) produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells
[2] The $AS01_B$ adjuvant is composed of the plant extract *Quillaja saponaria* Molina, fraction 21 (QS-21) (50 micrograms) and 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* (50 micrograms).
The powder is white.
The suspension is an opalescent, colourless to pale brownish liquid.

Indications/Uses

Shingrix is indicated for the prevention of herpes zoster (HZ) in adults aged 50 years or older and in adults aged 18 years or older at increased risk of HZ.

See “Warnings and Precautions” and “Properties/Effects”.
The use of Shingrix should be based on official vaccination recommendations.

Dosage/Administration

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Usual dosage

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 2 to 6 months later. The 2-month interval is preferable because of greater clinical experience.

Specific dosage

For individuals who are or might become immunodeficient or immunosuppressed due to disease or therapy and who would benefit from a shorter vaccination schedule, the second dose can be given 1 to 2 months after the initial dose (see “Pharmacodynamics”).
The need for booster doses has not been established.
Shingrix can be given with the same schedule in individuals previously vaccinated with live attenuated herpes zoster vaccine (see “Pharmacodynamics”).
Shingrix is not indicated for the prevention of primary varicella infection.

Children and adolescents

Safety and efficacy in individuals under 18 years of age have not been demonstrated.

Mode of administration

Shingrix is for intramuscular injection only, preferably in the deltoid muscle.
For instructions on reconstitution of the medicinal product before administration, see “Instructions for handling”.

Contraindications

Hypersensitivity to the active substances or to any component of the vaccine (see “Composition” and “Pharmaceutical form and active substance quantity per unit”).

Warnings and precautions

Prior to immunisation

It is good clinical practice to precede vaccinations with a review of the medical history (especially with regard to previous vaccinations and possible occurrence of undesirable events) and a clinical examination.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

As with other vaccines, vaccination with Shingrix should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

The vaccine is intended for prophylactic use only and not for the treatment of HZ disease.

In a post-marketing observational study in individuals aged 65 years or older, an increased risk of Guillain-Barré syndrome was observed during the 42 days following vaccination with Shingrix (see “Undesirable effects after market launch”).

Precautions for use

Do not administer the vaccine intravascularly, intradermally or subcutaneously.

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

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

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by various neurological symptoms such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from fainting.

There are no safety, immunogenicity or efficacy data to support replacing a dose of Shingrix with a dose of another HZ vaccine.

Limitations of the data

There are limited data to support the use of Shingrix in individuals with a history of HZ and in frail individuals including those with multiple comorbidities (see section “Properties/Effects”). Healthcare professionals therefore need to weigh the benefits and risks of HZ vaccination on an individual basis.

There are limited data on the efficacy and safety for the use of Shingrix in individuals at increased risk of HZ who are not recipients of autologous haematopoietic stem cell transplantation (aHSCT) (see “Properties/Effects”).

This medicinal product contains less than 1 mmol of sodium (23 mg) per vaccine dose, i.e. it is almost “sodium-free”.

This medicinal product contains potassium, but less than 1 mmol (39 mg) per vaccine dose, i.e. it is almost “potassium-free”.

Interactions

Use with other vaccines

Shingrix can be given concomitantly with unadjuvanted seasonal influenza vaccine, 23-valent pneumococcal polysaccharide vaccine (PPV23) or reduced-antigen diphtheria-tetanus-acellular pertussis vaccine (dTpa).

If Shingrix is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

The adverse reactions of fever and chills occurred more frequently when a PPV23 vaccine was administered at the same time as Shingrix.

Co-administration with other vaccines is not recommended due to lack of data.

Pregnancy, lactation

Pregnancy

There are no clinical data on use in pregnant women. Animal studies have not shown any direct or indirect toxic effects on pregnancy, embryonic development, development of the fetus and/or postnatal development (see “Preclinical data”). As a precaution, Shingrix should not be used during pregnancy.

Lactation

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

Fertility

Animal studies indicate no effects of Shingrix on male or female fertility.

Effects on ability to drive and use machines

No studies on the effects of Shingrix on the ability to drive and use machines have been performed.

Shingrix may have a minor effect on the ability to drive and use machines in the 2 to 3 days following the vaccination. Fatigue and malaise may occur following administration (see “Undesirable effects”).

Undesirable effects

Clinical trial data

The safety profile presented below is based on a pooled analysis of data generated in placebo-controlled clinical trials involving 5,887 participants aged between 50 and 69 years (Zoster-006) and 8,758 participants aged 70 and older (pooled Zoster-006/022) who received at least one dose of Shingrix. These data were generated in two placebo-controlled clinical trials (conducted in Europe,

North America, Latin America, Asia and Australia) where Shingrix was administered according to a 0-2-month schedule.
Additionally, in clinical trials, 1,587 subjects aged ≥ 18 years who were immunodeficient or immunosuppressed due to disease or therapy (referred to as immunocompromised) were vaccinated with at least one dose of Shingrix (placebo-controlled). Only limited data are available for adults aged 18-49 years at increased risk of HZ who are not immunocompromised.

Undesirable effects are listed below according to the following frequency: “very common” (≥ 1/10), “common” (≥ 1/100 to < 1/10), “uncommon” (≥ 1/1,000 to < 1/100), “rare” (≥ 1/10,000 to < 1/1,000), “very rare” (< 1/10,000).

The following table shows the frequency category of the undesirable effects reported in clinical trial data. The frequency category corresponds to the percentage of subjects reporting each adverse reaction following administration of Shingrix.

Frequency of undesirable effects

Undesirable effect		Frequency category	Older adults 50+ (%)	Immunocompromised subjects 18+ (%)
Blood and lymphatic system disorders				
Lymphadenopathy		Uncommon		
Nervous system disorders				
Headache		Very common	38	41[1]
Dizziness		Uncommon		
Gastrointestinal disorders				
Gastrointestinal symptoms (including nausea, vomiting, diarrhoea and/or abdominal pain)		Very common	17	46[2]
Musculoskeletal and connective tissue and bone disorders				
Myalgia		Very common	45	54[3]
Arthralgia		Uncommon		
General disorders and administration site conditions				
Injection site reactions	Pain	Very common	78	87[4]
	Redness		38	41[1]
	Swelling		26	23[1]

	Injection site pruritus	Common		
	Fatigue Chills Fever	Very common	45 27 21	70[2] 35[2] 25[1]
	Malaise	Common		

The reported frequencies for the very common undesirable effects in older adults ≥50 years of age (TVC with 7-day Diary card) and in immunocompromised subjects ≥18 years of age (TVC) correspond to the percentage of subjects with each adverse reaction within 7 days (Day 0 - Day 6) following vaccination, while for the other undesirable effects, the frequency category corresponds to the percentage of subjects with each adverse reaction within 30 days (Day 0 - Day 29) following vaccination (TVC).

Data for older adults ≥50 years of age are based on pooled data from studies Zoster-006 and Zoster-022.

Data for immunocompromised subjects ≥18 years of age are based on the highest reported frequency of each adverse reaction following administration of Shingrix in the studies Zoster-002, Zoster-028, Zoster-039, or Zoster-041.

[1] Zoster-039

[2] Zoster-028

[3] Zoster-002 and Zoster-028

[4] Zoster-041

Gout (including gouty arthritis) was reported by 0.18% (n = 27) versus 0.05% (n = 8) of subjects who received Shingrix or placebo, respectively, within 30 days of vaccination (pooled Zoster-006 and Zoster-022); available information is insufficient to determine a causal relationship with Shingrix.

In adults aged 50 years or over, the undesirable effects that were reported most frequently (percentage of subjects who reported the symptom at least once after vaccination) were injection site pain (78.0% of subjects overall; severe in 6.4% of subjects), myalgia (44.7% of subjects overall; severe in 5.1% of subjects), fatigue (44.5% of subjects overall; severe in 5.3% of subjects) and headache (37.7% of subjects overall severe in 3.3% of subjects). Most of these reactions did not last long (median duration of 2 to 3 days). The reactions that were reported as severe lasted 1 to 2 days.

Overall, there was a higher incidence of some adverse effects in younger age groups. In immunocompromised adult studies, there was a higher incidence of pain at the injection site, fatigue, myalgia, headache, shivering and fever in subjects aged 18 to 49 years compared with those aged 50 years and older. In older adult studies, there was a higher incidence of pain and swelling at the injection site, fatigue, myalgia, headache, shivering, fever and gastrointestinal symptoms in subjects aged 50 to 69 years compared with those aged 70 years and older.

In a clinical trial where 119 subjects aged ≥ 50 years were vaccinated with Shingrix following a 0-6-month schedule, the safety profile was similar to that observed in subjects vaccinated with Shingrix following a 0-2-month schedule.

Undesirable effects after market launch

Immune system disorders
Rare: hypersensitivity reactions including rash, urticaria, angioedema
Unknown: severe skin toxicity

Post-marketing observational study of the risk of Guillain-Barré syndrome (GBS) following vaccination with Shingrix
The association between vaccination with Shingrix and GBS was evaluated based on the claims data from the US federal health insurance program (Medicare) in people aged 65 years or older from October 2017 through February 2020. The risk of GBS following vaccination with Shingrix was assessed in self-controlled case series analyses using a risk window of 1 to 42 days post-vaccination and a control window of 43 to 183 days post-vaccination. The primary analysis found an increased risk of GBS during the 42 days following vaccination with Shingrix, with an estimated 3 excess cases of GBS per million doses administered to adults aged 65 years or older. In the secondary analysis, an increased risk of GBS during the 42 days following the first dose of Shingrix was observed, with an estimated 6 excess cases of GBS per million doses administered to adults aged 65 years or older, and no increased risk of GBS observed following the second dose of Shingrix. The available information is insufficient to determine a causal relationship with Shingrix.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Few administrations of a higher dose than recommended have been reported. No increase in reactogenicity or adverse reactions was reported.

Properties/Effects

ATC code

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

Mechanism of action

Shingrix is designed to induce an antigen-specific cellular and humoral immune response in individuals with pre-existing immunity to VZV.

Preclinical data show that $AS01_B$ induces a local and transient activation of the innate immune system through specific molecular pathways. This facilitates the recruitment and activation of antigen-presenting cells carrying gE-derived antigens in the draining lymph nodes, which in turn leads to the generation of gE-specific CD4+ T cells, CD8+ T cells and antibodies. The adjuvant effect of $AS01_B$ is the result of the interaction between MPL and QS-21 (plant extract from *Quillaja saponaria* Molina) formulated in liposomes.

Pharmacodynamics

Efficacy of Shingrix

Efficacy against Herpes Zoster (HZ) and Post-Herpetic Neuralgia (PHN)

Two phase III, placebo-controlled, observer-blind efficacy studies of Shingrix were conducted in adults aged ≥ 50 years with two doses administered two months apart:

- Zoster-006 (ZOE-50): total vaccinated cohort (TVC) of 15,405 subjects aged ≥ 50 years who received at least one dose of either Shingrix (N=7,695) or a placebo (N=7,710). PHN was not a primary endpoint in Zoster-006 and was only analyzed after completion of the study.
- Zoster-022 (ZOE-70): TVC of 13,900 subjects aged ≥ 70 years who received at least one dose of either Shingrix (N=6,950) or a placebo (N=6,950). With regard to PHN, the primary planned analysis was based on a pooled cohort of subjects aged ≥ 70 years from the Zoster-006 and Zoster-022 studies.

These studies were not designed to demonstrate the efficacy in subsets of frail individuals, including patients with multiple comorbidities. However, these individuals were not excluded from the studies.

Vaccine efficacy results against HZ and PHN, evaluated in the modified total vaccinated cohort (mTVC), are presented in Table 1 and Table 2. Participants who did not receive a second dose of the vaccine or who had a confirmed diagnosis of HZ within one month of the second dose were excluded from the analysis.

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

In the fourth year after vaccination, the efficacy against HZ was 93.1% (95% CI: 81.2; 98.2) and 87.9% (95% CI: 73.3; 95.4) in participants aged 50 years and older, and in participants aged 70 years and older respectively.

Interim results of Zoster-049 study (ongoing follow-up study of Zoster-006 and Zoster-022 studies) indicate that, at a mean follow-up time of approximately 7.1 years post vaccination, the efficacy against HZ was maintained up to 90.9% (95% CI: 88.16; 93.18) and 88.7% (95% CI: 84.50, 91.97) in

participants overall and aged ≥ 70 years respectively. These data are preliminary and may change at final analysis.

One phase III, placebo-controlled, observer-blind study (Zoster-002) evaluated the efficacy against HZ in autologous haematopoietic stem cell transplantation (aHSCT) recipients aged 18 years and older who received two doses of Shingrix 1-2 months apart. 1,846 subjects received at least one dose of either Shingrix (N=922) or a placebo (N=924) post-transplant. Zoster-002 included 694 subjects (completers 75.3% Shingrix) and 672 subjects (completers 72.7% placebo) until the end of the study. In the Shingrix and placebo group, 49 and 62 subjects, respectively, did not receive the second dose and 65 and 67 subjects, respectively, withdrew from the study during the first year due to serious adverse events (SAE). One subject in the placebo group and no subject in the Shingrix group were withdrawn from the study due to a SAE as assessed by the investigator.

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

Efficacy results from another study (Zoster-039), conducted in subjects with haematologic malignancies who also received two doses of Shingrix 1-2 months apart while receiving or after completion of cancer therapy, support the results of Zoster-002 study.

Vaccine efficacy results are presented in Table 1 and Table 2.

Table 1: Shingrix efficacy against HZ (mTVC)

Age (years)	Shingrix			Placebo			Vaccine efficacy (%) [95% CI]
	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1000 person years	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1000 person years	
ZOE-50*							
≥ 50	7,344	6	0.3	7,415	210	9.1	**97.2** [93.7; 99.0]
50-59	3,492	3	0.3	3,525	87	7.8	**96.6** [89.6; 99.4]
≥ 60	3,852	3	0.2	3,890	123	10.2	**97.6** [92.7; 99.6]
60-69	2,141	2	0.3	2,166	75	10.8	**97,4** [90.1; 99.7]
Pooled ZOE-50 and ZOE-70**							
≥ 70	8,250	25	0.8	8,346	284	9.3	**91.3** [86.8; 94.5]
70-79	6,468	19	0.8	6,554	216	8.9	**91.3** [86.0; 94.9]
≥ 80	1,782	6	1.0	1,792	68	11.1	**91.4** [80.2; 97.0]
Zoster-002* (aHSCT recipients#)**							
≥ 18	870	49	30.0	851	135	94.3	**68.2**

							[55.5; 77.6]
18-49	213	9	21.5	212	29	76.0	**71.8** [38.7; 88.3]
≥ 50	657	40	33.0	639	106	100.9	**67.3** [52.6; 77.9]

CI Confidence interval

* Over a median follow-up period of 3.1 years

** Over a median follow-up period of 4.0 years

Data in subjects ≥ 70 years of age are sourced from the pre-specified pooled analyses of ZOE-50 and ZOE-70 (mTVC), as these analyses provide the most robust estimates for vaccine efficacy in this age group.

*** Over a median follow-up period of 21 months

Antiviral prophylaxis in line with the local therapeutic standard was permitted

Approximately 13,000 subjects with underlying medical conditions, including conditions associated with a higher risk of HZ, were included in the Zoster-006 and Zoster-022 studies. A post-hoc analysis of efficacy against confirmed HZ undertaken in patients with common conditions (chronic kidney disease, chronic obstructive pulmonary disease, coronary heart disease, depression or diabetes mellitus) indicates that the vaccine efficacy is aligned with the overall efficacy against HZ.

Table 2: Shingrix efficacy against PHN

Age (years)	**Shingrix**			**Placebo**			**Vaccine efficacy (%)** [95% CI]
	Number of evaluable subjects	**Number of PHN* cases**	**Incidence rate per 1000 person years**	**Number of evaluable subjects**	**Number of PHN cases**	**Incidence rate per 1000 person years**	
ZOE-50**							
≥ 50	7,340	0	0.0	7,413	18	0.6	**100** [77.1; 100]
50-59	3,491	0	0.0	3,523	8	0.6	**100** [40.8; 100]
≥ 60	3,849	0	0.0	3,890	10	0.7	**100** [55.2; 100]
60-69	2,140	0	0.0	2,166	2	0.2	**100§** [< 0; 100]
Pooled ZOE-50 and ZOE-70***							
≥ 70	8,250	4	0.1	8,346	36	1.2	**88.8** [68.7; 97.1]
70-79	6,468	2	0.1	6,554	29	1.2	**93.0** [72.4; 99.2]
≥ 80	1,782	2	0.3	1,792	7	1.1	**71.2§** [< 0; 97.1]
Zoster-002** (aHSCT recipients #)**							
≥ 18	870	1	0.5	851	9	4.9	**89.3** [22.5; 99.8]
18-49	213	0	0.0	212	1	2.2	**100.0§** [< 0; 100.0]
≥ 50	657	1	0.7	639	8	5.8	**88.0**

							[10.4; 99.8]

* PHN was defined as zoster-associated pain rated ≥ 3 (on a scale of 0-10), persisting or appearing more than 90 days after onset of the zoster skin rash, using the "Zoster Brief Pain Inventory" (ZBPI)

CI Confidence interval

** Over a median follow-up period of 4.1 years

*** Over a median follow-up period of 4.0 years

Data in subjects ≥ 70 years of age are sourced from the pre-specified pooled analyses of ZOE-50 and ZOE-70 (mTVC), as these analyses provide the most robust estimates for vaccine efficacy in this age group.

**** Over a median follow-up period of 21 months

§ Not statistically significant

Antiviral prophylaxis in line with the local therapeutic standard was permitted

In Zoster-002, efficacy against HZ during a follow-up period that started one month after the second dose (corresponding to approximately six months after aHSCT) and continued until one year after aHSCT, when the HZ risk is highest, was 76.2% (95% CI: 61.1; 86.0).

Effect on HZ-associated pain

In adults aged 70 years and older with confirmed HZ, the use of HZ-associated pain medications was reported for 10 of 23 subjects (43.5%) who received Shingrix and for 160 of 223 subjects (71.7%) who received placebo.

In aHSCT adults aged 18 years and older with at least one confirmed HZ episode (Zoster-002), the median duration of severe ("worst") HZ-associated pain was 14 days in subjects receiving Shingrix and 24 days in subjects receiving placebo.

Immunogenicity of Shingrix

An immunological correlate of protection has not been established. The level of immune response that provides protection, including duration of protection, against HZ is therefore unknown.

In adults aged ≥ 50 years, the immune responses to Shingrix were evaluated in a subset of subjects from the phase-III efficacy studies Zoster-006 [humoral immunity and cell-mediated immunity (CMI)] and Zoster-022 (humoral immunity). The gE-specific immune responses (humoral and CMI) elicited by Shingrix one month after the second dose are presented in Tables 3 and 4.

Table 3: Humoral immunogenicity of Shingrix in adults aged ≥ 50 and ≥ 70 years (ATP cohort for immunogenicity)

Anti-gE immune response^								
	Month 3*				**Month 38****			
Age group (years)	**N (N')**	**VRR§ (%) (95% CI)**	**GMC (95% CI)**	**Median fold increase of concentration**	**N (N')**	**VRR§ (%) (95% CI)**	**GMC (95% CI)**	**Median fold increase of concentrations**

				s vs. pre-vaccination				vs. pre-vaccination (Q1; Q3)
Zoster-006								
≥ 50	1,070 (1,069)	98.5 (97.6; 99.1)	52,376.6 (50,264.1; 54,577.9)	41.9 (20.8; 86.9)	967 (952)	80.9 (78.2; 83.3)	11,919.6 (11,345.6; 12,522.7)	9.3 (4.9; 19.5)
Pooled Zoster-006 and Zoster-022								
≥ 70	742 (741)	96.6 (95.1; 97.8)	49,691.5 (47,250.8; 52,258.2)	34.3 (16.7; 68.5)	648 (637)	70.5 (66.8; 74.0)	10,507.7 (9,899.2; 11,153.6)	7.2 (3.5; 14.5)

ATP According to protocol

^ Anti-gE immune response = anti-gE antibody levels, measured by anti-gE enzyme-linked immunosorbent assay (gE ELISA)

* Month 3 = 1 month post-dose 2

** Month 38 = 3 years post-dose 2

N Number of evaluable subjects at the specified time point (for the GMC)

N' Number of subjects with pre-and post-result available at the specified timepoint (for the VRR and fold increase)

§ Vaccine response rate (VRR) for anti-gE is defined as the percentage of subjects who have at least a 4-fold increase in the post-dose 2 anti-gE antibodies concentration as compared to the pre-vaccination anti-gE antibodies (subjects seropositive at baseline), or as compared to the anti-gE antibodies cut-off value for seropositivity (subjects seronegative at baseline).

CI Confidence interval

GMC Geometric mean concentration

Q1, Q3 First and third quartiles

Table 4: Cell-mediated immunogenicity of Shingrix in adults aged ≥ 50 and ≥ 70 years (ATP cohort for immunogenicity)

gE-specific CD4[2+] T cell response^								
	Month 3*				**Month 38****			
Age group (years)	**N (N')**	**VRR§ (%) (95% CI)**	**Median frequency (Q1; Q3)**	**Median fold increase of frequency vs. pre-vaccination (Q1; Q3)**	**N (N')**	**VRR§ (%) (95% CI)**	**Median frequency (Q1; Q3)**	**Median fold increase of frequency vs. pre-vaccination (Q1; Q3)**
Zoster-006								
≥ 50	164 (149)	93.3 (88.0; 96.7)	1,844.1 (1,253.6; 2,932.3)	24.6 (9.9; 744.2)	152 (133)	52.6 (43.8; 61.3)	738.9 (355.7; 1'206.5)	7.9 (2.7; 31.6)
≥ 70***	52 (43)	88.4 (74.9; 96.1)	1,494.6 (922.9; 2,067.1)	33.2 (10.0; 1,052.0)	46 (38)	36.8 (21.8; 54.0)	480.2 (196.1; 972.4)	7.3 (1.7; 31.6)

ATP According to protocol

^ gE-specific CD4[2+] T cell response = gE-specific CD4+ T cell activity, measured by intracellular cytokine staining (ICS) assay (CD4[2+] T cells = CD4+ T cells expressing at least two of four selected immune markers)

* Month 3 = 1 month post-dose 2

** Month 38 = 3 years post-dose 2

N Number of evaluable subjects at the specified time point for the median frequency

N' Number of subjects with pre-and post-result available at the specified timepoint (for the VRR and fold increase)

§ Vaccine response rate (VRR) is defined as:
For initially subjects with pre-vaccination T cell frequencies below the cut-off, at least a 2-fold increase as compared to the cut-off (2x<320> Events/10E6 CD4+ T cells).
For initially subjects with pre-vaccination T cell frequencies above the cut-off, at least a 2-fold increase as compared to pre-vaccination T cell frequencies.

Q1, Q3 First and third quartiles

*** The gE-specific CD4[2+] data in the group aged ≥ 70 years were only generated in Zoster-006 because CD4+ T cell activity was not assessed in Zoster-022.

Data from a phase II, open-label, single-group, follow-up clinical study involving adults aged ≥ 60 years (Zoster-024) indicate that the vaccine-induced immune response (humoral and CMI) following a 0-2-month vaccination schedule persists until the 72nd month (approximately six years after the initial dose, i.e. 70 months after the second dose) (N= 119).
The mean anti-gE antibody concentration was more than seven times higher than the mean concentration in the pre-vaccination period. The mean frequency of gE-specific CD4[2+] T cells was more than 3.7 times higher than the frequency in the pre-vaccination period.

The humoral and CMI responses to Shingrix in immunocompromised adults aged ≥ 18 years were evaluated in the following studies:

- one Phase I/II study: Zoster-015 (HIV-infected subjects);
- one Phase II/III study: Zoster-028 (patients with solid tumours who underwent chemotherapy);
- three Phase-III studies: Zoster-002 (aHSCT recipients vaccinated after transplantation), Zoster-039 (patients with haematologic malignancies vaccinated during cancer treatment or following completion of cancer treatment) and Zoster-041 (kidney transplant recipients on chronic immunosuppressive treatment at the time of vaccination).

The gE-specific immune responses (humoral and CMI) elicited by Shingrix one month after the second dose in all immunocompromised populations studied are presented in Tables 5 and 6.

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

Anti-gE immune response^							
Month 2*				Month 13/18/25			
N (N‘)	VRR§ (%) (95% CI)	GMC (95% CI)	Median fold increase of concentrations vs pre-vaccination (Q1; Q3)	N (N‘)	VRR§ (%) (95% CI)	GMC (95% CI)	Median fold increase of concentrations vs pre-vaccination (Q1; Q3)
Zoster-002 (aHSCT recipients)							
82 (82)	67.1 (55.8; 77.1)	12,753.2 (7,973.0; 20,399.4)	14.1 (1.7; 137.0)	54 (52)	Month 13: 40.4 (27.0; 54.9)	Month 13: 3,183.8 (1,869.8; 5,421.2)	Month 13: 2.7 (1.0; 24.0)
				39 (38)	Month 25: 44.7 (28.6; 61,7)	Month 25: 2,819.0 (1,387.1; 5,729.1)	Month 25: 1.3 (0.6; 44.7)
Zoster-028 (solid tumour patients)							
87 (87)	86.2 (77.1; 92.7)	18,291.7 (14,432.1; 23,183.5)	21.5 (7.0; 45.2)	68 (68)	Month 13: 51.5 (39.0; 63.8)	Month 13: 4,477.3 (3,482.4; 5,756.3)	Month 13: 4.1 (2.1; 7.9)
Zoster-039 (hematologic malignancy patients)							
217 (217)	65.4 (58.7; 71.7)	13,445.6 (10,158.9; 17,795.6)	17.2 (1.4; 87.4)	167 (165)	Month 13: 52.1 (44.2; 59.9)	Month 13: 5,202.7 (4,074.8; 6,642.8)	Month 13: 5.1 (1.1; 17.0)
Zoster-041 (renal transplant recipients)							
121 (121)	80.2 (71.9; 86.9)	19,163.8 (15,041.5; 24,416.0)	15.1 (6.1; 35.0)	111 (111)	Month 13: 66.7 (57.1; 75.3)	Month 13: 8,545.1 (6,753.7; 10,811.5)	Month 13: 6.5 (3.1; 13.3)
Zoster-015 (HIV infected subjects)							
53 (54)	98.1 (89.9; 100)	42,723.6 (31,233.0; 58,441.6)	40.9 (18.8; 93.0)	49 (48)	Month 18: 91.7 (80.0; 97.7)	Month 18: 25,242.2 (19,618.9; 32,477.3)	Month 18: 24.0 (9.8; 39.7)

ATP According to protocol

^ Anti-gE immune response = anti-gE antibody levels, measured by anti-gE enzyme-linked immunosorbent assay (gE ELISA)

N Number of evaluable subjects at the specified time point (for the GMC)

N’ Number of subjects with pre-and post-result available at the specified timepoint (for the VRR and fold increase)

§ Vaccine response rate (VRR) for anti-gE is defined as the percentage of subjects who have at least a four-fold increase in the anti-gE antibodies concentration after the second dose compared to the anti-gE antibodies in the pre-vaccination period (subjects seropositive at baseline), or compared to the anti-gE antibodies cut-off value for seropositivity (subjects seronegative at baseline)

CI Confidence interval

GMC Geometric mean concentration

Q1; Q3 First and third quartiles

* Month 3 for Zoster-015

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

gE-specific CD4[2+] T cell response^							
Month 2*				Month 13/18/25			
N (N')	**VRR§ (%) (95% CI)**	**Median frequency (Q1; Q3)**	**Median fold increase of frequency vs. pre-vaccination (Q1; Q3)**	**N (N')**	**VRR§ (%) (95% CI)**	**Median frequency (Q1; Q3)**	**Median fold increase of frequency vs. pre-vaccination (Q1; Q3)**
Zoster-002 (aHSCT recipients)							
51 (42)	92.9 (80.5; 98.5)	6,644.9 (1,438.3; 13,298.6)	109.0 (34.4; 2,716.4)	32 (27)	Month 13: 70.4 (49.8; 86.2)	Month 13: 1,706.4 (591.4; 5,207.0)	Month 13: 43.6 (13.1; 977.8)
				30 (24)	Month 25: 70.8 (48.9; 87.4)	Month 25: 2,294.4 (455.2; 3,633.2)	Month 25: 50.9 (15.3; 515.2)
Zoster-028 (solid tumor patients)**							
22 (22)	50.0 (28.2; 71.8)	778.8 (393.1; 1,098.2)	4.9 (1.7; 33.0)	18 (17)	Month 13: 17.6 (3.8; 43.4)	Month 13: 332.9 (114.9; 604.6)	Month 13: 2.0 (1.3; 5.2)
Zoster-039 (hematologic malignancy patients)							
53 (43)	83.7 (69.3;93.2)	3,081.9 (1,766.2; 7,413.6)	45.9 (16.4; 2,221.9)	44 (33)	Month 13: 66.7 (48.2; 82.0)	Month 13: 1,006.7 (416.0; 3,284.5)	Month 13: 21.4 (7.5; 351.4)
Zoster-041 (renal transplant recipients)							
32 (28)	71.4 (51.3; 86.8)	2,149.0 (569.4; 3,695.1)	47.7 (14.7; 439.6)	33 (30)	Month 13: 56.7 (37.4; 74.5)	Month 13: 1,066.3 (424.8; 1,481.5)	Month 13: 16.9 (5.9; 211.4)
Zoster-015 (HIV infected subjects)							
41 (28)	85.7 (67.3;96.0)	2,809.7 (1,554.5; 4,663.7)	23.4 (8.5; 604.1)	49 (31)	Month 18: 64.5 (45.4;80.8)	Month 18: 1,533.0 (770.0; 2643.1)	Month 18: 12.0 (5.7; 507.0)

ATP According to protocol

^ gE-specific CD4[2+] T cell response = gE-specific CD4+ T cell activity, measured by intracellular cytokine staining (ICS) assay (CD4[2+] T cells = CD4+ T cells expressing at least two of four selected immune markers)

§ Vaccine response rate (VRR) is defined as:

For initially subjects with pre-vaccination T cell frequencies below the cut-off, at least a 2-fold increase as compared to the cut-off (2x<320> Events/10E6 CD4+ T cells).

For initially subjects with pre-vaccination T cell frequencies above the cut-off, at least a 2-fold increase as compared to pre-vaccination T cell frequencies

N Number of evaluable subjects at the specified time point for the median frequency

N' Number of subjects with pre-and post-result available at the specified timepoint (for the VRR and fold increase)

Q1; Q3 First and third quartiles

* Month 3 for Zoster-015

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

Immunogenicity in subjects with a history of HZ prior to vaccination

Subjects with a history of HZ were excluded from Zoster-006 and Zoster-022.

In a phase III, uncontrolled, open-label clinical study (Zoster-033), 96 adults ≥ 50 years of age with a physician-documented history of HZ received 2 doses of Shingrix 2 months apart. Laboratory confirmation of HZ cases was not part of the study procedures. The anti-gE GMC at 1 month after the last vaccine dose was 47,758.7 mIU/mL (95% CI: 42,258.8; 53,974.4).

There were 9 reports of suspected HZ in 6 subjects over a one-year follow up period. This is a higher recurrence rate than generally reported in observational studies in unvaccinated individuals with a history of HZ. A causal relationship with Shingrix was not established.

Immunogenicity in subjects receiving 2 doses of Shingrix 6 months apart

In a phase III, open-label clinical study (Zoster-026) where 238 subjects ≥ 50 years of age were randomised to receive 2 doses of Shingrix 2 or 6 months apart, the vaccine response rate (anti-gE antibodies) one month after vaccination following the 0-6-month schedule was 96.5% (95% CI: 90.4; 99.2).

The humoral immune response (anti-gE antibodies concentration) following the 0-6-month schedule was not inferior to the humoral immune response following the 0-2-month schedule, as the 97.5% CI upper limit of the antibodies concentration ratio was below 1.50 [1.16 (97.5% CI: 0.98; 1.39)].

The anti-gE antibodies concentration one month after the last vaccine dose was 38,153.7 mIU/ml (95% CI: 34,205.8; 42,557.3) following the 0-6-month schedule and 44,376.3 mIU/ml (95% CI: 39,697.0; 49,607.2) following the 0-2-month schedule.

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

In a phase III, open-label, multicenter clinical study (Zoster-048), 430 adults ≥ 65 years of age with or without a previous history of vaccination with live attenuated HZ vaccine ≥ 5 years earlier were group-matched at a 1:1 ratio to receive 2 doses of Shingrix 2 months apart. The immune response to Shingrix was unaffected by prior vaccination with live attenuated HZ vaccine.

Clinical efficacy

See under “Pharmacodynamics”.

Pharmacokinetics

An evaluation of pharmacokinetic properties is not required for vaccines.

Absorption

Not applicable.

Distribution

Not applicable.

Metabolism

Not applicable.

Elimination

Not applicable.

Preclinical data

Pharmacology and/or toxicology studies on animals
Preclinical data reveal no special hazard for humans based on conventional studies with Shingrix or $AS01_B$ of acute and repeated dose toxicity, local tolerance and cardiovascular/respiratory safety pharmacology.
Reproductive toxicity
Administration of VZV gE $AS01_B$ to female rats did not indicate any harmful effects with respect to fertility, pregnancy, embryo**-**foetal development, parturition or postnatal development.
The treatment of male rats did not affect mating performance, fertility or early embryonic development.
Further studies on reproductive toxicity with MPL, QS-21 or $AS01_B$ in rats or rabbits revealed no findings that give cause for concern at clinical doses.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.
For shelf life after reconstitution of the medicinal product, see “Instructions for handling”.

Special precautions for storage

Store in a refrigerator (2-8°C) in the original package to protect from light and keep out of the reach of children. Do not freeze.

For storage conditions after reconstitution of the medicinal product, see “Instructions for handling”.

Instructions for handling

The powder and suspension must be reconstituted prior to administration.

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

How to prepare Shingrix:

1. Withdraw the entire contents of the vial containing the suspension into a syringe.
2. Add the entire contents of the syringe into the vial containing the powder.
3. Shake gently until the powder is completely dissolved.

The reconstituted vaccine is an opalescent, colourless to pale brownish liquid.

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

After reconstitution, the vaccine should be used promptly. If this is not possible, the vaccine should be stored in a refrigerator (2-8°C). If not used within 6 hours, the vaccine should be discarded.

Before administration:

1. Withdraw the entire contents of the vial containing the reconstituted vaccine into a syringe.
2. Change the needle and use a new needle to administer the vaccine.

Any unused medicinal product or waste material must be disposed of in accordance with national requirements.

Authorisation number

67987 (Swissmedic)

Packs

1 vial with powder and 1 vial with suspension (B)

10 vials with powder and 10 vials with suspension (B)

Marketing authorisation holder

GlaxoSmithKline AG, 3053 Münchenbuchsee

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