Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Recombinant Varicella Zoster Virus (VZV) glycoprotein E (gE) antigen

Proprietary Product Name: Shingrix

Sponsor: GlaxoSmithKline

December 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
Ab	Antibody
AE	Adverse event
AML	Acute myeloid leukaemia
$AS01_B$	Adjuvant System containing 50 µg MPL, 50 µg QS-21 and liposomes
ATP	According-To-Protocol
CBER	Center for Biologics Evaluation and Research (FDA)
CD4	Cluster of differentiation marker 4
CD8	Cluster of differentiation marker 8
CHMP	Committee for Medicinal Products for Human Use (EMA)
CI	Confidence interval
CMI	Cell mediated immunity
CRP	C-reactive protein
CSR	Clinical Study Report
DOPC	Dioleoyl Phosphatidylcholine
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency, EU
EOS	End of study
EU	European Union
FDA	Food and Drug Administration, US
FLU-D-QIV	GlaxoSmithKline's unadjuvanted quadrivalent seasonal influenza vaccine
GCP	Good Clinical Practice
gE	Glycoprotein E (of varicella zoster)
GMC	Geometric mean concentration

Abbreviation	Meaning
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
HCT	Haematopoietic stem cell transplant
HIV	Human immunodeficiency virus
HZ	Herpes zoster
HZ/su	Herpes zoster subunit candidate vaccine (50 µg gE/ AS01 B), also called gE/AS01$_B$ candidate vaccine
IC	Immunocompromised
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN-γ	Interferon gamma
IL-2	Interleukin 2
IM	Intramuscular
LL	Lower limit
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre
MPL	3-O-desacyl-4'-monophosporyl Lipid A
mTVC	Modified Total Vaccinated Cohort
PCR	Polymerase chain reaction
PHN	Post-herpetic neuralgia
pIMD	Potential immune-mediated disease
PIP	Paediatric Investigation Plan
QS-21	QS-21 Stimulon (*Quillaja saponaria* Molina fraction 21)
RMP	Risk Management Plan
RR	Risk ratio
SAE	Serious adverse event

Abbreviation	Meaning
SC	Subcutaneous
SMQ	Standardised MedDRA Query
TVC	Total Vaccinated Cohort
UL	Upper limit
US	United States
VE	Vaccine efficacy
VHP	Vaporized hydrogen peroxide
VRR	Vaccine response rate
VZV	Varicella zoster virus
WBC	White blood cells
WHO	World Health Organization
ZBPI	Zoster Brief Pain Inventory
µg	Microgram
µL	Microliter

I. Introduction to product submission

Submission details

Type of submission:	New biological medicine
Decision:	Approved
Date of decision:	27 June 2018
Date of entry onto ARTG:	2 July 2018
ARTG number:	289257
Active ingredient:	Recombinant varicella zoster virus glycoprotein E antigen
Product name:	Shingrix
Sponsor's name and address:	GlaxoSmithKline Australia Pty Ltd PO Box 18095 Melbourne VIC 8003
Dose form:	Powder for injection vial with solution for suspension vial
Strength:	50 µg
Containers:	vials
Pack size:	1
Approved therapeutic use:	*Shingrix is indicated for the prevention of herpes zoster and post herpetic neuralgia in adults 50 years of age or older.*
Route of administration:	Intramuscular
Dosage:	The primary vaccination schedule consists of two doses of 0.5 mL each; an initial dose followed by a second dose 2 to 6 months later. The need for booster doses has not been established. Shingrix is not indicated for prevention of primary varicella infection. Administration is via intramuscular injection only, preferably in the deltoid muscle.

Product background

This AusPAR describes the application by GlaxoSmithKline Australia Pty Ltd (GSK) (the sponsor) to register Shingrix recombinant varicella zoster virus glycoprotein E antigen vaccine powder for injection vial with suspension for suspension vial for the following indication:

> *Shingrix is indicated for the prevention of herpes zoster (HZ) and HZ related complications, such as post herpetic neuralgia (PHN), in adults 50 years of age or older.*

Shingrix, also referred to as herpes zoster subunit vaccine (HZ/su)[1], is designed to induce antigen specific cellular and humoral immune responses in individuals with pre-existing immunity against varicella zoster virus (VZV).

The varicella zoster virus (VZV) is a DNA virus of the herpes virus family. The primary infection with VZV, varicella, causes a diffuse vesicular rash or chickenpox. Clinical resolution is followed by the establishment of latent infection within the sensory dorsal root ganglia. Reactivation of this neurotropic virus, believed to be due to a decline in cellular immunity, leads to herpes zoster (HZ), or shingles, a painful, unilateral vesicular eruption in a restricted dermatomal distribution.

Herpes zoster can be a debilitating illness with a significant risk of complications, particularly in the immunocompromised, and there are limited treatment options. The currently available vaccine, Zostavax, has a moderate protective efficacy of 51% in adults 60 years of age or older. Zostavax is a live attenuated vaccine and so is contraindicated in immunocompromised patients who are at particular risk of herpes zoster. Therefore, there is an evident clinical place for a vaccine which can be used in this patient group, as well as for a vaccine with higher clinical efficacy.

Shingrix is an adjuvanted recombinant VZV glycoprotein E (gE) subunit vaccine. This vaccine does not contain live virus. Glycoprotein E (gE) was selected for the vaccine antigen as it is the most abundant viral surface glycoprotein in VZV virions and VZV infected cells, plays a central role in VZV infection and is an important target of VZV specific cellular and humoral immune responses.

The adjuvant AS01 contains the immunostimulants QS-21 (*Quillaria saponaria* Molina 21) and monophosphoryl lipid A (MPL) combined with liposomes. It was stated that this adjuvant is being tested in other investigational vaccines.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 2 July 2018.

At the time the TGA considered this application, a similar application had been approved in countries as shown in Table 1.

[1] HZ/su: The Herpes Zoster subunit vaccine (50 µg gE/ $AS01_B$), also called gE/$AS01_B$ vaccine.

Table 1: List of countries in which Shingrix application had been submitted/ approved

Country	Submission /approval dates	Indication
European Union (centralised procedure)	Submission: 25/11/2016 Approval (Date of issue of marketing authorisation valid throughout the European Union): 21/03/2018	Shingrix is indicated for prevention of herpes zoster (HZ) and post herpetic neuralgia (PHN), in adults 50 years of age or older (see section 5.1). The use of Shingrix should be in accordance with official recommendations.
USA	Submission: 21/10/2016 Approval: 20/10/2017	Shingrix is a vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. Limitations of Use (1): Shingrix is not indicated for prevention of primary varicella infection (chickenpox).
Canada	Submission: 14/11/2016 Approval: 13/10/2017	Shingrix is indicated for prevention of herpes zoster (HZ, or shingles) in adults 50 years of age or older (see Clinical Trials section).
Japan	Submission: 18/04/2017 Approval: 23/03/2018	Prevention of herpes zoster (HZ) Precaution (s) for indication (s) This vaccine should not be administered as a varicella vaccine based on the Preventive Vaccination Law.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

Table 2 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Table 2: Timeline for Submission PM-2017-01784-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	28 June 2017

Description	Date
First round evaluation completed	11 December 2017
Sponsor provides responses on questions raised in first round evaluation	12 February 2018
Second round evaluation completed	27 April 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	1 May 2018
Sponsor's pre-Advisory Committee response	14 May 2018
Advisory Committee meeting (ACV 8)	30 May 2018
Registration decision (Outcome)	27 June 2018
Completion of administrative activities and registration on ARTG	2 July 2018
Number of working days from submission dossier acceptance to registration decision*	207

*Statutory timeframe for applications is 255 working days

III. Quality findings

Introduction

Shingrix, referred to as herpes zoster subunit vaccine (HZ/su), is designed to induce antigen specific cellular and humoral immune responses in individuals with pre-existing immunity against varicella zoster virus (VZV).

Shingrix vaccine is composed of recombinant varicella zoster virus glycoprotein E antigen (50 micrograms) powder and suspension for suspension for injection vial. The glycoprotein E antigen is produced in Chinese hamster ovarian (CHO) cells.

The varicella zoster virus glycoprotein E (VZV gE) is the most abundant virion envelope glycoprotein and the predominant VZV glycoprotein expressed on the surface of VZV infected cells. A truncated form of the VZV gE, lacking the coding sequences for the hydrophobic transmembrane domain and the C-terminal cytoplasmic tail, is produced by recombinant DNA technology in CHO-K1 cells. Elimination of the transmembrane anchor domain-coding sequence facilitates the secretion of the recombinant protein.

Drug substance (active ingredient)

The drug substance of the recombinant VZV glycoprotein E (gE) purified bulk is produced by using a cell culture, harvested via filtration, and purified through a series of purification

steps, including chromatography columns. After post purification filtration, the purified bulk is stored at -45 ± 10°C.

One single cell culture provides one single harvest (intermediate) on which one single clarification is performed. From this, one single purification is performed to obtain one batch of gE purified bulk antigen.

The manufacturing is performed according to good manufacturing practice (GMP) requirements.

There were no issues pertaining to manufacture or manufacturer of the product.

The release specifications for gE purified bulk are according to company specifications. There were no issues pertaining to specifications.

Drug product

The vaccine is provided as a lyophilised powder in a vial with a suspension solution used for suspension of the powder in a separate vial.

The gE purified bulk substance is formulated and tested against the nominated specifications prior to sterile filtration and aseptic filling into vials followed by lyophilisation.

The suspension solution is formulated and tested prior to filling into vials.

The proposed shelf life of the vaccine is 36 months at +2°C/+8°C and protected from light.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product and to establish a shelf life. The real time data submitted support the shelf life of 36 months when stored at +2°C/+8°C in the original packaging to protect from light.

In-use stability data have also been submitted. The proposed shelf life and storage conditions for the reconstituted vaccine are 6 hours when stored at + 2°C to + 8°C.

Regarding the transportation of this vaccine to Australia:

- The company has confirmed that all batches of Shingrix will be transported to Australia within the required storage temperature of + 2 to + 8°C.
- However, the stability data for temperature cycling studies were provided to support the temperature excursions from + 2/+ 8°C storage conditions. The product exposure up to 14 days at 25°C during the 36 months shelf-life is acceptable.

The stability studies were performed according to the ICH Q1E.[2]

Quality summary and conclusions

There are no outstanding quality issues in regards to approval of Shingrix.

[2] ICH Q1E: ICH harmonised tripartite guideline evaluation for stability data.

IV. Nonclinical findings

Introduction

The sponsor has applied to register a new biological entity, a non-live zoster vaccine consisting of the recombinant subunit varicella zoster virus (VZV) glycoprotein E (gE) and the $AS01_B$[3] adjuvant system (Shingrix, also referred to as $gE/AS01_B$). Shingrix is proposed to be used for the prevention of herpes zoster (HZ) and HZ related complications, such as post herpetic neuralgia, in adults 50 years of age or older. The proposed regimen involves two doses of 0.5 mL each, by intramuscular (IM) injection; an initial dose followed by a second dose 2 to 6 months later. The need for a booster dose has not been established. Shingrix is not indicated for prevention of primary varicella infection.

General comments

Shingrix is an adjuvanted recombinant VZV-glycoprotein E (gE) subunit vaccine. This vaccine does not contain live virus (unlike the current registered Zostavax, which is not approved for use in immunocompromised individuals since it is a live virus vaccine).

The gE antigen is a purified recombinant protein produced in Chinese Hamster Ovary (CHO) cells. The gE protein is provided in a lyophilized form in mono dose vials (50 µg/dose). The $AS01_B$ (liquid) adjuvant system is provided in separate mono dose vials (0.5 ml/dose). $AS01_B$ contains 50 µg of each of the immuno-enhancers QS-21 (*Quillaja saponaria* Molina, fraction 21) and monophosphorlyl lipid A (MPL, 3-O-desacyl-4'-monophosphoryl lipid A) combined with liposomes.

The sponsor has submitted nonclinical studies of the candidate vaccine, adjuvant alone or components of the adjuvant (MPL and QS-21). In the nonclinical studies the component QS-21 was evaluated alone as detoxified QS-21(DQ), in which cholesterol was added to reduce the known haemolytic activity of QS-21 which is seen when QS-21 is administered without cholesterol. QS-21 (DQ) was used in primary pharmacodynamics and Good Laboratory Practice (GLP) toxicology testing of QS-21. In the vaccine formulation QS-21 is added post formation of the liposome and is associated with the liposomes through its interaction with cholesterol. MPL is not a new excipient. Studies with MPL alone have been previously evaluated in the Cervarix evaluation report (Submission PM-2006-0544-2-1), and thus they are not reviewed in this report.

Pharmacology

Since there is no appropriate animal model to study VZV pathogenesis, latency or reactivation, no nonclinical data to demonstrate protection against HZ by vaccine candidates (that is challenge studies) were submitted. Nonclinical pharmacology studies were limited to demonstration of immunogenicity and this is considered acceptable under these circumstances. Other primary pharmacology studies were conducted for the selection of an adjuvant, supporting manufacturing changes during development and investigating the mode of action of the adjuvant system. In addition, safety pharmacology studies were conducted with $gE/AS01_B$, $AS01_B$ and MPL.

[3] AS01B: Adjuvant System containing 50 µg MPL, 50 µg QS-21 and liposomes

Primary pharmacology

gE/AS01$_B$

gE/AS01$_B$ has been designed to induce both cellular and humoral immune responses. In the nonclinical studies both humoral and T cell (CD4+ and CD8+) responses were evaluated following injection of the recombinant gE protein formulated with different adjuvants systems (including oil-in-water emulsions ± MPL ± QS-21 (ASO2, ASO3), MPL + Alum (ASO4), and liposomes + MPL + QS-21 at different quantities (AS01)) in mice.

Significantly higher titres of gE-specific antibodies and CD4+ T cell responses were observed in VZV primed mice injected with any adjuvant system compared to gE protein alone indicating the requirement of an adjuvant in this vaccine. At 1/10th of the human dose gE (5 µg)/AS01$_B$ induced superior cellular immune responses, measured as interferon gamma (IFN-γ) and/or interleukin 2 (IL-2) producing CD4 T cells, compared to other adjuvant systems (including MPL alone, QS-21+MPL without dioleoyl phosphatidylcholine (DOPC), MPL+AlumOH). The selection of AS01$_B$ as the adjuvant was supported by the immunogenicity data. High antibody titres to gE were also detected in rabbits after 3 subcutaneous (SC) or IM doses of the vaccine in the repeat dose toxicity studies. These studies lacked efficacy data (protection against HZ) and would need to be addressed in the clinical studies.

Various gE/AS01$_B$ lots (gE antigen produced at different manufacturing scales, including the final scale; and lots used in clinical efficacy and clinical consistency campaigns) generated comparable immune responses in terms of gE specific antibody titres and frequency of gE-specific cytokine producing CD4+ T cells in mice (IFN-γ ± IL-2 producing T cells isolated from the spleen). The geometric mean ratios and the estimated 95% confidence intervals are within the predefined equivalence limits of 0.5 to 2.

During the production of gE commercial lots, higher levels of gE methionine oxidation were observed compared to the clinical consistency lots, which was attributed to a transient exposure of gE final bulk to vaporized hydrogen peroxide (VHP) residues prior to the lyophilisation step. Artificial oxidation of gE in gE final bulk had no effect on humoral or cellular immunity in mice in terms of levels of gE-specific antibodies and frequencies of gE specific cytokine producing CD4+ T cells (IFN-γ ± IL-2 producing T cells isolated from the spleen). The geometric mean ratios and the estimated 95% confidence intervals (CI) were within the predefined limits of 0.5 to 2 CI.

In mice, SC route of administration of gE/AS01$_B$ induced lower (by approximately 1.4 fold) humoral and cellular immune responses than the IM injection, statistically non-significant for CD4+ T cell response and statistically significant for antibody response.

AS01, QS-21 and MPL

The mechanism of action of AS01 and individual components QS-21 and MPL was studied. The AS01 adjuvant system differs from other licensed vaccine adjuvants in terms of ability to enhance antigen specific T cell response in several model antigen systems (gE, HBs, OVA). Activation of the innate immune system by AS01 was transient and mediated via TLR4 signalling for MPL. For QS-21, the signalling pathways were not fully elucidated but involved caspase 1/inflammasome activation, and it enters cells via endocytosis and then traffics to lysosomes. The maximum adjuvant effect of AS01 on adaptive response, especially T cell response, required spatio-temporal co-localization of AS01 with the antigen, consistent with an early and locally acting mechanism of the adjuvant. A combination of MPL and QS-21 in AS01 induced a synergistic response, characterized by increased or sustained cytokine levels, associated with a more efficient induction of an adaptive response. MPL contributed to the early cytokine response in the muscle while QS-21 played a role in the early cytokine response in the draining lymph node. The early IFN-γ secretion produced by NK cells within 6 h post immunisation, resulted from a

synergy between MPL and QS-21. IFN-γ signalling pathway plays a major role in adjuvant effect of $AS01_B$ by enhancing early cytokine production, immune cell recruitment and activation after immunisation with $AS01_B$ adjuvanted vaccines. MPL and QS-21 induces a diversified population of activated antigen presenting cells, responsible for T cell priming, driven by the specific ability of MPL and QS-21 to activate DC and monocytes respectively. These data support addition of both immune enhancers in the liposome adjuvant formulation.

Safety pharmacology

Safety pharmacology studies covered only the cardiovascular and respiratory systems using full human dose. No effects on these systems were observed following intravenous (IV) administration of the complete vaccine (1 mL/kg) in rats (200 x the human dose based on µg/kg body weight for gE, approximately 36 x the human dose on µg/m^2 body surface area basis of adjuvants) or following IM administration of $AS01_B$ adjuvant alone (0.5 mL/animal) in dogs (approximately 3 x the human dose on µg/m^2 body surface area basis) and IV injection of $AS01_B$ in rats (1 mL/kg, approximately 36 x the human dose on µg/m^2 body surface area basis).

Effects on the central nervous system were not specifically studied for the new adjuvant system, but repeat dose toxicity studies showed no signs of neurological toxicity.

Pharmacokinetics

Pharmacokinetic studies are not required for vaccines as per the guideline;[4] and the World Health Organization (WHO) guideline on nonclinical testing of vaccines. The sponsor has provided bio-distribution studies of the adjuvants.

The bio-distribution of [^{14}C]QS-21 and [^{14}C]DOPC was analysed after a single IM administration in an AS01-like formulation in mice. DOPC and QS-21, formulated in AS01, were distributed most notably to the draining lymph nodes and the liver. QS-21 and DOPC were rapidly cleared from the injection site and became progressively dissociated from each other. Bio distribution studies with a single IM administration of QS-21 in an aqueous solution in rabbits also showed wide distribution throughout the body.

Greater than 99% QS-21 was eliminated via renal excretion within 72 hours. Only 2% DOPC was excreted via urine and the low recovery (18% of dose) after 72 hours suggested that DOPC was excreted via the expired air or faecal excretion (faecal excretion not examined) or retained in the body.

Toxicology

Nonclinical toxicity studies were undertaken with the vaccine gE/$AS01_B$, the $AS01_B$ Adjuvant System and its individual immune-enhancers QS-21 and MPL. Most studies were done in rat and rabbit, both demonstrating a good antibody response. The toxicity studies were mostly performed by the IM route of administration since this is the proposed route of administration for licensure. Toxicity studies were also conducted by the SC route of administration to support a specific clinical trial.

Acute toxicity

The single dose toxicity of gE/$AS01_B$, $AS01_B$ and QS-21 was assessed as part of the local tolerance toxicity studies and is discussed in the local tolerance section.

[4] CHMP/SWP/465/95; Note for Guidance on preclinical pharmacological and toxicological testing of vaccines.

Repeat-dose toxicity

Repeat dose toxicity studies with the vaccine were adequately conducted. The use of a single species (rabbit) is consistent with the relevant guidelines and demonstration of good immunogenicity which supports the use of this species as an appropriate animal model for toxicity (note rabbits were not used in pharmacodynamic studies). The toxicity studies were generally performed by the IM route which is the clinical route. Vaccine testing in both sexes and group sizes were appropriate. Repeat dose testing with $AS01_B$ and QS-21 administered by the IV route in rats and rabbits were also adequately conducted.

Exposure ratios have been calculated based on dose per kg body weight (µg/kg) for the varicella antigen and per body surface area (µg/m^2) for the adjuvant QS-21 present in $AS01_B$. The number of doses administered to the animals in the repeat dose toxicity studies exceeded the number of doses proposed in the clinic and the doses administered were greater than the proposed clinical dose which is adequate (see Table 3 below).

Table 3: Dose and relative exposure in repeat dose toxicity studies

Study	Species	Treatment Regimen	Dose			Exposure ratio#	
			gE Ag (µg/kg)	QS-21 (µg/kg)	QS-21 (µg/m2)†	gE Ag	QS-21
$gE/AS01_B$							
[information redacted]	Rabbit	3 doses (IM) 2 week intervals	33	17	204	17	6
[information redacted]		4 doses (SC/IM) 2 week intervals	17	17	204	17	6
$AS01_B$							
[information redacted]	Rat	7 doses (IM) 2 week intervals	-	80	480	-	15
[information redacted]	Rabbit	5 doses (IM) 2 week intervals	-	17	204	-	6
QS-21							
[information redacted]	Rat	6 doses (IM) 3-4 day intervals	-	10/16‡	60/96‡	-	2/3‡
			-	50/80‡	300/480‡	-	9/15‡
			-	100/160‡	600/960‡	-	18/29‡
[information redacted]	Rabbit	6 doses (IM) 3-4 day intervals	-	7	84	-	2.5
			-	33	396	-	12
			-	67	804	-	24
Proposed clinical use	Human	2 doses (IM) 2-6 months apart	1*	1*	33	-	-

† conversion factor from mg/kg to mg/m2 6 for rats, 12 for rabbits, 33 for humans; # Animal/human dose in mg/kg for gE Ag and in mg/m2 for QS-21; * 50 µg dose and assuming 50 kg body weight; ‡ male/female

gE-AS01$_B$

The vaccine was well tolerated in both the 6 and 8 week repeat dose studies, where rabbits were administered, 33 times the human dose (µg/kg) for the antigen and 6 times the human dose (µg/m^2) for the adjuvant, either by IM or SC route, 3 or 4 doses at 2 week intervals. Local inflammatory changes at the injection site were produced as expected which was reversible. Other treatment related changes included a transient increase in fibrinogen, white blood cells (WBC) (mainly neutrophils) and C-reactive protein (CRP), a decrease in albumin/globulin ratio and activated response of the draining popliteal and inguinal lymph nodes. These responses are generally related to the inflammatory process following vaccination and no other significant safety issues were identified. There was also an increase in plasma bilirubin (only total bilirubin was measured), which was probably secondary to haemolysis induced by the adjuvant (see also discussion below). No distinct differences in systemic effects between the routes of administration in rabbits (IM versus SC) but microscopically, the SC injections caused less reaction (in both incidences and severity) at the site of injection than IM.

AS01$_B$ alone

Repeat dose toxicity studies were conducted by administering 7 injections of AS01$_B$ in rats and 5 injections in rabbits by the IM route at 2 week intervals (15 and 6 x the human dose based on µg/m^2 body surface area, respectively). Findings were similar to those with the complete vaccine, gE/AS01$_B$. Acute inflammatory response at the injection site was observed in all the animals. Transient increases in WBC (mainly neutrophil), increase in fibrinogen, decrease in albumin/globulin ratio, increase in CRP and increased body temperature (observed in rats only) were probably related to the local inflammation or the immune stimulation following AS01$_B$ injection. Small increases in plasma bilirubin (only total bilirubin was measured) were observed in rats, and were probably secondary to haemolysis induced by the adjuvant. Significant but small decreases in haemoglobin concentration, haematocrit, red blood cell count, mean corpuscular volume and mean corpuscular haemoglobin were observed in male rats. These parameters returned to normal values 28 days after the injection.

QS-21(DQ) alone

Repeat dose toxicity studies were conducted by administering 6 injections of DS-12 (DQ) (2 to 29 times or 3 to 24 times the human dose per injection, based on µg/m^2 body surface area in rats and rabbits, respectively) by IM route at 2 week intervals. Repeat doses were well tolerated by both the animals and only caused transient effects on haematology and clinical chemistry and a higher mean body temperature in the high dose group 24 hours after the first injection in the rabbits, as observed with AS01$_B$. Microscopically, some inflammatory response was observed at the injection sites, with complete recovery after 28 days.

Genotoxicity

The sponsor did not provide genotoxicity data for the final vaccine formulation gE/AS01$_B$, which is considered acceptable as per guidelines. In accordance with the EMEA guidelines, a standard battery of genotoxicity studies was conducted for the adjuvant, AS01$_B$ and its component QS-21. Different batches of AS01$_B$ by IV or IM administration did not show any evidence of causing chromosomal damage or bone marrow cell toxicity. IM3 (AS01$_B$end of filling) at 14 times the human dose (µg/m^2) did not induce micronuclei in rats, but caused a decrease in immature erythrocytes in the bone marrow, suggesting bone marrow toxicity. A follow up study of AS01$_B$ with the same dose and dosing schedule as the micronucleus test (that is 0.2 mL/day for 2 days, 14 times the human dose on a µg/m^2 body surface area basis) showed no bone marrow toxicity. Instead, bone marrow pro-erythrocytes increased slightly on Day 13 (not on Day 3), while late normoblasts

decreased (note no difference was observed in early or intermediate normoblasts). This would indicate no interference by $AS01_B$ in early stages of red cell production. Slight decreases in peripheral blood (haemoglobin, packed cell volume, mean corpuscular haemoglobin, mean corpuscular volume), a slight increase in reticulocytes, higher incidence of abnormal red cell forms (anisocytosis, hypochromasia and macrocytosis) and cell clumping were observed in the treated groups and were probably due to direct effects of the adjuvant on peripheral erythrocytes, as observed in repeat dose toxicity studies with $AS01_B$ and QS-21.

$AS01_B$ was not tested for mutagenicity in bacteria or mammalian cells. QS-21(DQ) and QS-21 were non-mutagenic in bacterial mutation tests and gene mutation of cultured mouse lymphoma cells *in vitro*. The test concentration of QS-21 (DQ) was low (up to 100 µg/plate in the bacterial assay and 10 µg/mL in the mammalian cell assay) due to the presence of liposomes (cholesterol and DOPC), but the concentration of QS-21 (non-DQ form) in another bacterial assay was adequate. No test article related chromosomal damage and/or damage to the mitotic spindle apparatus of the bone marrow target cells was observed in male rats treated by IV administration of the maximum (tolerable) dose of QS-21 (DQ) containing up to 160 µg QS-21/kg (which is 29-fold greater than the human dose on a $\mu g/m^2$ surface area basis), although it is worth noting distribution of QS-21 to the bone marrow was not explicitly demonstrated in this study). Generally these data support the lack of genotoxic potential of $gE/AS01_B$.

Carcinogenicity

Carcinogenicity studies were not performed as per guideline.

Reproductive toxicity

The vaccine and adjuvants were evaluated for effects on male and female fertility, embryofetal development, and pre and postnatal development in rats and rabbits. Numbers of animals used, study design, IM route of administration and duration were appropriate. Doses and relative exposures are shown in Table 4.

Table 4: Dose and relative exposure in reproductive toxicity studies

Species	Study (Study no.)	Treatment regimen	Dose			Exposure ratio#	
			gE Ag (µg/kg)	QS-21 (µg/kg)	QS-21 (µg/m²) †	gE Ag	QS-21
gE/AS01$_B$ and AS01$_B$							
Rat	Male fertility [information redacted]	42, 28 and 14 days prior to mating	40	40	240	40	7
	Female fertility, embryofetal and pre-postnatal development [information redacted]	28 and 14 days before mating, gestation Day 3, 8, 11 and 15, and lactation Day 7	80	80	480	80	15
QS-21 (DQ)							
Rat	Female fertility, embryofetal & pre-postnatal development [information redacted]	28 and 14 days before mating, gestation Day 3, 8, 11 and 15, and lactation Day 7	-	16, 80, 160	96, 480, 960	-	3, 15, 29
Rabbit	Female fertility, embryofetal & pre-postnatal development (AB14898)	28 and 14 days before mating, gestation Day 3, 8, 11 15 and 24, and lactation Day 7	-	7, 33, 67	84, 396, 804	-	2.5, 12, 24
Human	-	2 doses 2-6 months apart	1*	1*	33	-	-

† conversion factor from mg/kg to mg/m2 6 for rats, 12 for rabbits, 33 for humans; # Animal/human dose in mg/kg for gE Ag and in mg/m2 for QS-21; * 50 µg dose and assuming 50 kg body weight

Treatment of male rats with 40 µg/kg gE in AS01$_B$ (40 times the clinical dose on µg/kg body weight basis) or up to 80 µg/kg adjuvant AS01$_B$ alone (7 times the human dose on a µg/m² body surface area basis) 3 times before mating did not affect male mating performance, fertility, early embryonic development or male reproductive organs (histopathology and sperm analysis). Female rats treated with 0.2 ml Shingrix (80 µg gE in AS01$_B$, 80 times the clinical dose on a µg/kg body weight basis) or 80 µg/kg adjuvant AS01$_B$ (15 times the human dose on a µg/m² body surface area basis) twice before mating and then on Days 3, 8, 11 and 15 of gestation and on Day 7 of lactation showed slight, transient swelling at the injection site with no adverse effect on embryo-fetal or pre- and post-natal survival, growth or development of the offspring up to 25 days of age.

Two reproductive studies on QS-21 (DQ) involving IM administration in rats and rabbits were conducted, for the rats with the same dosing regimen as the study with the vaccine in rats discussed above, for rabbits including an additional treatment time point at gestation Day 24. In the rat, QS-21, at up to 160 µg/kg (29 times the human dose on a µg/m² body surface area basis), did not adversely affect female fertility, embryo-fetal or pre and post-natal survival, growth or development of the offspring up to 25 days of age. However, rabbits dosed with 67 µg/kg QS-21 (24 times the human dose on a µg/m² body surface area basis) had a significant maternal mean body weight loss associated with reduced mean food consumption at the end of the gestation period. Lower mean fetal weight was

also noted. There were no treatment related effects on embryofetal development at the mid-dose, 33 µg/kg (12 times the clinical dose on a µg/m^2 body surface area basis).

Postnatal development up to 25 days of age was unaffected in rats or rabbits. Potential effects by the vaccine or adjuvants on development from weaning to sexual maturity were not assessed.

Pregnancy classification

The sponsor has proposed Pregnancy Category B2.[5] There are no data on the use of Shingrix in pregnant women. Available data in rabbits dosed with adjuvant QS-21 at 67 µg/kg showed no evidence of an increased occurrence of fetal damage besides lower fetal weight associated with maternal toxicity and therefore category B2 is appropriate.

Local tolerance

The Shingrix vaccine formulation or AS01$_B$ (0.5 mL, 17 times the human dose on a µg/kg body weight basis) administered by a single IM or SC injection was evaluated in a local tolerance study in rabbits. Extra muscular, mononuclear cell infiltration at the injection site was observed in all animals administered the vaccine by the IM route. The observed slight inflammation at the injection sites is considered a direct consequence of an anticipated pharmacological action resulting from the stimulation of the immune system. Animals administered by the SC route revealed slight to severe diffuse mixed inflammatory cell infiltration in all treated animals. Local tolerance studies in rats and rabbits demonstrated that IM injections with QS-21 (DQ) (up to 160 µg/kg in rats and 67 µg/kg in rabbits, 67 to 160 times the human dose of QS-21 on a mg/kg body weight basis) showed dose dependent local inflammatory reactions at the injection site, similar to those observed with AS01$_B$ or the adjuvanted vaccine. In the repeat dose toxicity studies, local inflammatory reactions were completely or partially reversible 4 weeks after the last dose.

Paediatric use

Shingrix is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Comments on the Nonclinical Safety Specification of the Risk Management Plan

Results and conclusions drawn from the nonclinical program for Shingrix detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the nonclinical evaluator.

Nonclinical summary and conclusions

- The sponsor has generally conducted adequate studies on pharmacology and toxicity of the vaccine and its adjuvant AS01$_B$ (which contains 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and a novel component, *Quillaja saponaria* Molina extract, fraction 21 (QS-21) formulated in liposomes consisting of dioleoylphosphatidylcholine (DOPC) and cholesterol). All safety pharmacology, repeat dose toxicity, genotoxicity and reproductive toxicity studies for the vaccine and adjuvants were performed under GLP

[5] Pregnancy Category B2 is defined as Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

conditions. The composition of the nonclinical dossier submitted met regulatory guidelines for vaccines/adjuvants.

- Pharmacodynamic studies examined the immune response of gE formulated with various adjuvant systems (ASO2, ASO3), MPL + Alum (ASO4), and liposomes + ML + QS-21 at different quantities (AS01). $AS01_B$ was selected based on its superior ability to induce cellular immune responses, measured as IFN-γ and/or IL-2 producing CD4 T cells, compared to other adjuvant systems. The mechanism of action of $AS01_B$ and individual components were demonstrated to be immune enhancers in the liposome formulation. However, these pharmacodynamic studies lacked efficacy data (protection against HZ via challenge studies) due to the limitation of animal models and would need to be addressed in the clinical studies.
- Safety pharmacology studies assessed effects of $gE/AS01_B$ (in rats) and $AS01_B$ (in rats and dogs) on the cardiovascular and respiratory systems. No adverse effects were detected on cardiovascular or respiratory functions in any animal. Repeat dose toxicity studies showed no signs of neurological toxicity.
- Repeat dose toxicity studies of $gE/AS01_B$ by the IM and SC route were conducted in rabbits (3 to 4 doses with 2 week dosing intervals) and $AS01_B$ and QS-21 by the IM route in rats and rabbits (5 to 7 doses). The vaccine and adjuvant were well tolerated. All vaccine treated animals developed anti-gE antibodies. The expected local inflammatory changes at the injection site and related inflammatory response were the main findings associated with the treatment. The doses of the gE antigen was 33 times the clinical dose on a mg/kg basis and of the adjuvant up to 29 times the clinical dose on a $\mu g/m^2$ body surface area basis. Transient effects on haematology and clinical chemistry and a higher mean body temperature in the high dose group were related to the immunostimulatory activity or mild haemolytic effects of the adjuvant. All changes were partially or completed reversible.
- $AS01_B$ and QS-21 produced no genetic damage in the standard battery of genotoxicity tests.
- Shingrix by IM injection in rats at adequate antigen doses did not affect male or female fertility, embryofetal development or postnatal development of offspring up to 25 days age. Similarly, the adjuvant QS-21 by IM administration to rats did not affect female fertility, embryofetal development or postnatal development of offspring up to 25 days age.
- In rabbits dosed with QS-21 at 67 μg/kg (24 times the clinical dose on a $\mu g/m^2$ body surface area basis) by IM injection 28 and 14 days prior to mating, on gestation Days 3, 8, 11, 15 and 24 and on lactation Day 7, decreased fetal weights were observed, and were associated with maternal toxicity (body weight loss during gestation and decreased food consumption). There were no embryofetal effects at 33 μg/kg (12 times the human dose on a $\mu g/m^2$ body surface area basis). Reproductive toxicity of Shingrix was not studied in rabbits.
- Local tolerance study with the vaccine showed inflammatory reactions, expected immune response to the vaccine antigen and adjuvant at the injection site, as observed in the repeat dose studies.

Conclusions and recommendation

- The nonclinical data provided was satisfactory.
- The primary pharmacology studies adequately demonstrated sero-conversion of animals to virus antigen present in the vaccine tested in presence of the $AS01_B$ adjuvant. However, due to the limitation of an adequate animal model to determine

the efficacy of the vaccine, protection against HZ would need to be established by clinical studies.

- Adequate repeat dose toxicity and local tolerance studies with Shingrix vaccine and the adjuvant did not raise safety issues.
- Studies in rats and rabbits showed no reproductive toxicity. An Australian Pregnancy Category B2 is recommended.
- There are no nonclinical objections to the vaccine registration provided protection against HZ is demonstrated by clinical data.
- The nonclinical evaluator also made comments regarding the draft PI but these are beyond the scope of the AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The varicella-zoster virus (VZV) is a DNA virus of the herpes virus family. The primary infection with VZV, varicella, causes a diffuse vesicular rash or chickenpox. Clinical resolution is followed by the establishment of latent infection within the sensory dorsal root ganglia. Reactivation of this neurotropic virus, believed to be due to a decline in cellular immunity, leads to herpes zoster (HZ), or shingles, a painful, unilateral vesicular eruption in a restricted dermatomal distribution. A prodromal phase may occur 2 to 3 days prior to the appearance of the rash. This may include headache, photophobia, malaise and itching, tingling or pain in the affected dermatome. The rash is typically self-limiting lasting 10 to 15 days.

The Australian Immunisation Handbook states that approximately 490 cases per 100,000 population of HZ are reported annually in Australia for all ages, while in those aged 50 years and over the rate is approximately 1000 cases per 100,000 population. The incidence rises with age from an estimated rate of 652 per 100,000 person years in persons aged 50 to 59 years to 1,450 per 100,000 person years in persons aged 70 to 79 years (ATAGI 2017).[6] Using general practice data, the annual incidence of HZ in the 60+ age group was estimated at 15.4 per 1,000 persons.[7] The increased risk with advancing age is believed due to declining cell mediated immunity.

Apart from age, other risk factors for HZ are disorders of cell mediated immunity and immunosuppression from any cause including human immunodeficiency virus (HIV) and immunosuppressive medications, as well as physical trauma, underlying malignancy, and chronic lung or renal disease. The rates of HZ are up to 15 times higher in those who are immunocompromised due to HIV infection, and in the first year following haematopoietic stem cell transplantation up to 30% of patients may develop HZ.

[6] Australian Technical Advisory Group on Immunisation (ATAGI). *The Australian immunisation handbook* 10th ed (2017 update). Canberra: Australian Government Department of Health, 2017.
[7] MacIntyre R, et al. Increasing Trends of Herpes Zoster in Australia. *PLoS ONE* 2015; 10(4): e0125025

Complications are estimated to occur in 13 to 26% of patients with HZ. The most frequent is post herpetic neuralgia (PHN).which is neuropathic pain persisting after the rash has healed.[8]

The risk of PHN increases with age up to about 1 in 5 of those aged over 80 years compared to 1 in 10 of those aged 50 to 59 years. Other complications included ophthalmic disease, neurological complications (for example meningoencephalitis and myelitis), secondary bacterial skin infection, scarring and pneumonia. Disseminated HZ may develop rarely and is more common in the immunocompromised.

Current treatment options

Treatment during the acute phase of herpes zoster is with oral antiviral therapy which can hasten healing of lesions and decrease the duration and severity of neuritis. Treatment needs to be given within 72 hours of rash onset. The Australian Immunisation Handbook notes:

> 'that antiviral therapy, if initiated within 3 days of the onset of HZ, has been shown to reduce the severity and duration of HZ and may reduce the risk of developing PHN. However, despite medical therapy, PHN may persist for years and can be refractory to treatment.'

Those with complicated herpes zoster may require intravenous and or prolonged therapy.

In terms of prophylaxis there is currently one herpes zoster vaccine available in Australia; Zostavax. This is a lyophilised preparation of the Oka/Merck strain of live, attenuated VZV given as a single dose regimen. The approved indication is:

> *Zostavax is indicated for the prevention of herpes zoster (shingles) in individuals 50 years of age and older.*
>
> *Zostavax is indicated for the prevention of postherpetic neuralgia (PHN) and for reduction of acute and chronic zoster-associated pain in individuals 60 years of age and older.*

Vaccination with Zostavax is not indicated for the treatment of herpes zoster or PHN.

The Shingles Prevention Study was a randomised, double blind, placebo controlled efficacy study of the frozen formulation of Zostavax conducted in 38,546 adults aged ≥ 60 years. The protective efficacy of Zostavax against herpes zoster was 51% (95% CI: 44 to 58%). Efficacy was greater in those aged 60 to 69 years than those aged 70 years and over (64% versus 38%). Efficacy against PHN was similar in both age groups at 66 to 67% (Zostavax PI). In a further large study in adults 50 to 59 years, the protective efficacy of Zostavax was 69.8% (95% CI: 54.1 to 80.6%). The effect of Zostavax on PHN was not evaluated in the latter trial (Zostavax PI).

Clinical rationale

Herpes zoster can be a debilitating illness with a significant risk of complications, particularly in the immunocompromised, and there are limited treatment options. The currently available vaccine, Zostavax, has a moderate protective efficacy of 51% in adults 60 years of age or older. This vaccine is a live attenuated vaccine and so is contraindicated in immunocompromised patients who are at particular risk of herpes zoster. Therefore,

[8] PHN occurs when acute neuropathic pain associated with HZ evolves into a chronic, debilitating pain. PHN is conventionally defined as chronic pain that persists for at least 3 months (≥90 days) after rash onset and can include pain that appears ≥3 months after rash onset.

there is an evident clinical place for a vaccine which can be used in this patient group, as well as for a vaccine with higher clinical efficacy.

The sponsor stated that the VZV antigen glycoprotein E (gE) was selected for the vaccine antigen as 'it is the most abundant viral surface glycoprotein in VZV virions and VZV infected cells, plays a central role in VZV infection and is an important target of VZV specific cellular and humoral immune responses'.

The adjuvant AS01 contains the immunostimulants QS-21 (*Quillaria saponaria* 21) and monophosphoryl lipid A (MPL A) combined with liposomes. It was stated that this adjuvant is being tested in other investigational vaccines.

Guidance

In the Clinical Overview, the sponsor stated that during the clinical development of the vaccine several regulatory consultations took place on a number of topics with the European Medicines Agency(EMA), the Food and Drug Administration (FDA) (US), the Pharmaceuticals and Medical Device Agency (Japan), and with national competent authorities in selected EU countries and in Canada.

Relevant guidelines for this dossier include:

- EMEA/CHMP/VEG/134716/2004; Guideline on adjuvants in vaccines for human use.
- EMEA/CHMP/VMP/164653/2005; Guideline on clinical evaluation of new vaccines.

The clinical development program was compliant with these guidelines.

Contents of the clinical dossier

The dossier documented a full clinical development program for a vaccine.

The clinical dossier contained a tabular list of clinical studies, literature references, documents relating to clinical assay validation, Integrated Summary of Safety, patient narratives and the clinical study reports (including the main report, amendments and annexes) for the following 19 studies:

- Phase I:
  - Study EXPLO-CRD-004; Phase I/II exploratory study with varicella vaccine
  - Study ZOSTER-018, -019; Phase I/II extension studies of EXPLO-CRD-004
  - Study ZOSTER-023; Phase I study in adults of Japanese ethnic origin.
- Phase II
  - Study ZOSTER-003; antigen dose selection study
  - Study ZOSTER-011, -012, -013; extension studies of Study ZOSTER-003 for Years 1, 2 and 3
  - Study ZOSTER-024; extension study of Study ZOSTER-003 to Year 6
  - Study ZOSTER-010; adjuvant dose selection study.
- Phase III in healthy adults
  - Study ZOSTER-006; pivotal efficacy and safety in ≥ 50 year olds
  - Study ZOSTER-022; pivotal efficacy and safety in ≥ 70 year olds
  - Study ZOSTER-004; co-administration with influenza vaccine
  - Study ZOSTER-007; lot-to-lot consistency study

- Study ZOSTER-026; schedule comparison study
- Study ZOSTER-032; route of administration study (SC versus IM)
- Study ZOSTER 033; adults with previous HZ.

· Phase I/II Immunocompromised adults

- Study ZOSTER-001; autologous haematopoietic stem cell transplant recipients
- Study ZOSTER-015; HIV infected adults.

The submission also contained Clinical Overview, Summaries of Clinical Efficacy and Clinical Safety, list of literature references and synopses of individual studies.

Paediatric data

The dossier did not include paediatric data. The sponsor stated that a Paediatric Investigation Plan (PIP) for the vaccine has been approved in July 2013 by the EU Paediatric Committee for *'prevention of Varicella Zoster Virus reactivation'* and the target indication is '*prevention of herpes zoster in immunocompromised subjects'.* A waiver for infants from birth to less than one year of age has been granted on the grounds that the reactivation of varicella zoster virus does not occur in the youngest paediatric population. The two agreed studies will be initiated if a positive benefit-risk balance in immunocompromised adults is achieved.

Good clinical practice

The Clinical Overview states that all trials were conducted in accordance with the principles of Good Clinical Practice (GCP) as well as local regulatory and ethical requirements.

One site in Mexico which enrolled subjects in Studies ZOSTER-006 and ZOSTER-022 was found to have significant and widespread deviations from GCP and subjects from this site were excluded from analyses. The numbers involved were 671/16,160 (4.15%) and 865/14,816 (5.84%) in the respective studies.

Pharmacokinetics

Pharmacokinetic studies are not relevant for vaccines (EMEA guidelines) therefore no studies were performed with the herpes zoster vaccine (HZ/su).

Pharmacodynamics

Studies providing pharmacodynamic data

Pharmacodynamic data for the vaccine comprises of its immunogenicity in terms of the vaccine induced humoral immune response and the cell mediated immune (CMI) response.

CMI response was only assessed during early phase development to select vaccine formulation. This was due to specialised procedures and blood volume required. Humoral immune response was then assessed as measured by anti-gE enzyme linked immunosorbent assay (ELISA).

The sponsor stated in the Clinical Overview that 'a moderately positive correlation has been observed between humoral immune responses as measured by anti-gE ELISA and CMI responses as measured by the sponsor's antigen specific CMI assay.'

Table 5: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID
Primary Pharmacology	Cell Mediated Immunity	EXPLO-CRD-004
	Cell Mediated Immunity	ZOSTER-OO3
	Humoral Immunity	ZOSTER-003
	Humoral Immunity	ZOSTER-023
	Humoral Immunity	ZOSTER-007
	Humoral Immunity	ZOSTER-032
Secondary Pharmacology	Effect on Lymphoproliferation	EXPLO-CRD-004
	Effect on Memory B cells	EXPLO-CRD-004
	Effect on Memory B cells	ZOSTER-018
	Effect on Memory B cells	ZOSTER-019
Gender other genetic and Age Related Differences in PD Response	Effect of gender	No studies
	Effect of age	ZOSTER-003
	Japanese subjects	ZOSTER-023
PD Interactions	Haematopoietic stem Cell Transplant (HCT)	ZOSTER-001
	HIV / antiretrovirals	ZOSTER-015
Population PD and PK-PD analyses	No studies	
	No studies	

Evaluator's conclusions on pharmacodynamics

HZ/su, given by IM route according to a 2 dose schedule, induced robust antigen specific immune responses in adults ≥ 50 years of age that were consistently high 1 month post Dose 2 in all age strata. Immune responses were also robust in adults ≥ 70 years although with increasing age, there appears to be a trend to slightly lower anti-gE Antibody (Ab) and CMI responses and more rapid waning of immune responses. The strong immune response, both cell mediated and humoral, is important due to the declining immunity in the elderly population. While the antigen specific immunogenicity decreased shortly after vaccination, it remained above pre-vaccination levels over at least 6 years. It is currently not known whether efficacy will persist over a longer period of time and if, in case of diminishing efficacy, additional doses will be required to maintain protection by boosting the immune response of previously vaccinated individuals.

Based on the immunogenicity data in a limited number of immune compromised adults (autologous haematopoietic stem cell transplant (HCT) or with HIV infection), the vaccine

was shown to be immunogenic in this population. Further studies in a larger population are necessary before more definite conclusions can be drawn. An indication in immunocompromised subjects is not being sought in this application.

There are currently no immunological correlates of protection for the HZ/su vaccine.

Consistency in terms of anti-gE Ab response was demonstrated between three HZ/su lots formulated from commercial-scale gE and $AS01_B$

The proposed PI reflects the information from the pharmacodynamics studies conducted.

Dosage selection for the pivotal studies

Phase II dose finding studies

gE antigen dose finding studies

Study EXPLO CRD-004 found that two doses of 50 µg gE increased the immune response over a single dose and from this 50 µg gE was used as the reference dose of Study ZOSTER-003. A lower dose (25 µg) and higher dose (100 µg) were then also included in the study to assess antigen dose.

Study ZOSTER-003 was a Phase II, single blind, randomised, controlled, multicentre vaccination study which evaluated the safety and immune response of HZ/su in 715 healthy adults aged 60 to 69 and ≥ 70 years. The study compared 3 doses (25, 50 or 100 µg) of gE with $AS01_B$ adjuvant when administered as 2 doses (at 0,2 months) compared to 2 doses of 100 µg gE/Saline or a single dose of 100 µg gE/$AS01_B$ to select the optimal antigen dose and schedule of the candidate HZ vaccine for use in future trials. A total of 715 subjects were enrolled in the study and randomised in a 1:3:3:3:3 ratio with stratification by age in a 1:4 ratio (60 to 69 and ≥ 70 years of age). The primary objective was to compare the gE-specific CD4+ T cell response in gE/$AS01_B$ study vaccine groups at Month 3 in older adults (≥ 70 years).

The gE antigen dose selection was based on assessment of CD4 T cell response to gE (secreting at least 2 different cytokines upon stimulation with gE) at Month 3 following two doses of vaccine.

The sponsor stated that cell mediated immune response data were used for the primary assessment rather than humoral immunogenicity *as CMI is considered to play a critical role in controlling symptomatic VZV reactivation*. The evaluator agrees with this selection.

Study ZOSTER-003 found similar CMI responses with both the 50 µg and 100 µg antigen doses together with similar reactogenicity. Therefore the lower dose of 50 µg was selected for further development.

The presence of $AS01_B$ resulted in a superior immune response but also increased incidence of adverse events (AEs).

Adjuvant dose finding studies

Study ZOSTER-010

Study ZOSTER-010 was a Phase II, observer blind, randomised, placebo controlled vaccination study which evaluated the immunogenicity of gE/$AS01_B$ vaccine in comparison to gE combined with half dose $AS01_B$ adjuvant (gE/AS01E), un-adjuvanted gE (gE/saline) and placebo in 410 healthy adults aged ≥ 50 years (mean of 65 years). Subjects were randomised 4:4:2:1 respectively and received two doses of administered two months apart.

The sponsor concluded that, while there was higher reactogenicity with $AS01_B$, the rates were deemed 'clinically acceptable'.

Given the improved immunogenicity of the higher dose adjuvant the evaluator agrees with the conclusions.

Reactogenicity was higher in the younger age groups.

The symptom rates are relatively high and this could possibly impact on compliance with Dose 2 of the vaccine schedule.

The sponsor has been asked to comment whether a lower adjuvant dose was considered for younger adults.

Study ZOSTER-003

Study ZOSTER-003 found that CD4 T cell response to vaccine containing adjuvant was greater than 100 µg gE/saline for both median frequencies and also the proportion of responders.

Dose number, schedule and route

Dose number

Study ZOSTER-003 also assessed immunogenicity responses after 1 and 2 vaccinations. The CD4 T cell response after the first dose increased 2.4 to 3.1 fold compared to pre-vaccination levels for subjects who received 25, 50 or 100 µg $gE/AS01_B$ vaccine and following the second vaccination at Month 3 there was a further 3.5 to 4.8 fold increase. When comparing one to two doses of 100 µg $gE/AS01_B$, it was found that the CMI response (median frequency of gE-specific CD4(2+) T cells) was greater with two doses in both the 60 to 69 and ≥ 70 year old age groups. Humoral immune response was also notably greater with two doses.

These data were supported by Study ZOSTER-010, where there was also a consistent increase in CMI response after the second vaccination of $gE/AS01_B$. Similarly, in Study EXPLO CRD-004 a second dose of vaccine induced better CD4 T cell response and higher antibody levels than 1 dose of vaccine.

Dose schedule

Study ZOSTER-026

Study ZOSTER-026 was an open label, randomised, parallel group immunogenicity study which assessed two vaccination intervals longer than 2 months (0, 6 and 0, 12 months) in 354 adults ≥ 50 years of age. As measured by the anti-gE antibody geometric mean concentration (GMC) ratio one month post second vaccination, the 0 and 6 month schedule was found to be non-inferior to the 0,2 month schedule, however the 0 and12 month vaccination interval did not meet the non-inferiority criterion (GMC ratio upper limit (UL) of the 97.5% CI < 1.5).

Route

Study ZOSTER-032

Study ZOSTER-032 was a Phase III, randomised, open label, single site clinical trial to assess the safety and immunogenicity of HZ/su vaccine when administered subcutaneously (SC) as compared to intramuscularly (IM) according to a 0,2 month schedule in 60 Japanese adults aged ≥ 50 years.

The study was not statistically powered to allow between group comparisons.

The study found similar immune responses (GMC and vaccine response rate (VRR)) at Month 3 between SC and IM administration. However, the local reactogenicity

(particularly Grade 3 redness and swelling) of the SC was much higher than the IM administration.

Due to the reactogenicity, the sponsor discontinued development of the SC indication.

Evaluator's conclusions on dose finding for the pivotal studies

In Study ZOSTER-003, there was a similar CMI response and reactogenicity with both the 50 µg and 100 µg antigen doses. The 25 µg gE dose was inferior to the higher doses in terms of CMI response. Therefore, the dose of 50 µg was selected for further development.

The presence of $AS01_B$ adjuvant resulted in a superior immune response but also increased reactogenicity. The full dose $AS01_B$ resulted in an increased immune response (CMI and humoral) compared to half strength dose and was selected for further development.

Based on the presented clinical immunogenicity data, the evaluator agrees with the sponsor's dose selection for use in the Phase III program.

Two doses of vaccine resulted in an improved response compared to a single dose (Studies ZOSTER-003, ZOSTER-026 and EXPLO CRD-004). While the vaccine dosing interval could be extended to 6 months based on non-inferior immunogenicity data, until there are data linking immunogenicity to efficacy the evaluator believes that only the 2 month dosing interval should be recommended. A 12 month interval is not recommended.

Subcutaneous administration was associated with high local reactogenicity and development was ceased.

Efficacy

Pivotal or main efficacy studies

There were two studies providing efficacy data: Studies ZOSTER-006 and ZOSTER-022. Other studies in the dossier provided immunogenicity data. Study ZOSTER-006 included subjects aged ≥ 50 years and Study ZOSTER-022 included subjects aged ≥ 70 years. The studies ran concurrently at the same sites. The clinical study report (CSR) for Study ZOSTER-022 contained analysis of pooled data from the two studies. The sponsor stated that the design of the two studies was agreed upon with regulatory agencies in Europe, the US and Japan.

As specified in the protocol, if both studies met their primary endpoint (efficacy against HZ) then the pooled data analysis for HZ and PHN was to be undertaken. This pooled analysis was the primary analysis for efficacy against PHN in adults ≥ 70 years of age.

Pooling of data was acceptable due to the studies having the same design and methodologies, inclusion and exclusion criteria, treatment groups and evaluations. An analysis of correlates of protection from Studies ZOSTER-006 and ZOSTER-022 was planned but could not be located in the dossier. A question has been raised by the evaluator.

Evaluator commentary

In Study ZOSTER-006, in the modified Total Vaccinated Cohort (mTVC), the HZ/su vaccine was found to be highly efficacious in preventing HZ in subjects aged ≥ 50 years with a vaccine efficacy (VE) of 97.16% (95% CI: 93.72% to 98.97%). The result was consistent when analysis was undertaken at the final HZ analysis and at the end of study (EOS) time points. It was also supported by Total Vaccinated Cohort (TVC) and According-To-Protocol

(ATP) population analyses. Vaccine efficacy was consistent across age groups of 50 to 59, 60 to 69 and ≥ 70 years.

The overall VE for PHN in adults ≥ 50 years was 100% (95% CI: 77.1 to 100.0%) although the study was not powered for this endpoint. PHN efficacy was seen in the 50 to 59 and ≥ 70 year age groups however no conclusions were possible in the 60 to 69 years of age group due to a lack of cases. It was also not possible to draw conclusions on other secondary endpoints due to the low numbers in the HZ/su group. There was no HZ related mortality and no HZ related hospitalisations in the HZ/su group. There were no significant effects on pain or pain medication use.

Immunogenicity data from a subset of subjects showed a strong anti-gE antibody response and CMI response, with some decline over 3 years, nonetheless levels remained higher than pre vaccination levels. Data were consistent across age groups and study regions.

In Study ZOSTER-022, VE in the prevention of HZ was confirmed in the elderly population (≥ 70 years of age) after a median follow up period of 3.9 years. Efficacy was high at 89.8% (95% CI: 84.3 to 93.7%, $p < 0.0001$) and consistent across the two age subgroups (70 to 79 and ≥ 80 years). PHN VE was also found in this study (85.5%, 95% CI: 58.5 to 96.3%) although the study was not powered for this.

A reduction in duration of pain was not confirmed despite a reduction in duration of pain medication use. High efficacy and resultant small case numbers meant secondary endpoints could not be confirmed.

There was a strong humoral immune response across the age subgroups (70 to 79 and ≥ 80 years of age).

Pooled analysis of Studies ZOSTER-006 and ZOSTER-022 found results consistent with the individual studies. In the prespecified analysis, for subjects aged ≥ 70, the HZ/su vaccine was efficacious in preventing HZ 91.3% (95% CI: 86.9 to 94.5%) with consistent results for both the 70 to 79 and ≥ 80 years of age groups.

Efficacy was also demonstrated for PHN in the ≥ 70 years of age (88.8%, 95% CI: 68.7 to 97.1%). The low numbers in the ≥ 80 years of age group meant that VE for PHN in this group could not be demonstrated. For those with HZ, there was no significant reduction in the incidence of PHN (VE of 0.3%, 95% CI: -161.5% to -65.6%), although case numbers were very small. These results mean that vaccine efficacy in preventing PHN is most likely due to the effect against HZ.

The sponsor has been asked to comment on the impact on PHN efficacy if different definitions of pain duration were used (rather than 90 days).

A post-hoc analysis of the pooled data found a reduction in risk complications other than PHN. Consequently the proposed indication includes the broad wording '*prevention of HZ and HA-related complications such as PHN*'. The evaluator does not agree with the inclusion of complications other than PHN in the indication as the statement has been based on a post-hoc analysis with low power and such complications can have varying mechanisms and pathogenesis.

Long term follow up studies will be needed to demonstrate efficacy against HZ and PHN beyond 4 years and this may be addressed by the follow up Study ZOSTER-049 which is currently ongoing.

In general, quality of life data in subjects experiencing an episode of HZ did not demonstrate any notable differences between treatment groups.

Other immunogenicity studies

Study ZOSTER-026

Study ZOSTER-026 was a Phase III, randomised, open label, uncontrolled, parallel group study to assess the safety and immunogenicity of HZ/su vaccine when administered according to a 0 and 2 month, 0 and 6 month or 0 and 12 month schedule in adults aged ≥ 50 years. It was conducted between March 2013 and April 2015 at one site in the US and one in Estonia.

Study ZOSTER-033

Study ZOSTER-033 was a Phase III, non-randomised, open label, multicentre clinical trial to assess the immunogenicity and safety of HZ/su vaccine when administered intramuscularly on a 0,2 month schedule to adults ≥ 50 years of age with a history of a prior episode of HZ. The study was conducted between June 2013 and November 2014 in Canada and Russia.

Study ZOSTER-004

Study ZOSTER-004 was a Phase III, randomised, open label, controlled, multicentre study which assessed the immunogenicity and safety of HZ/su when co-administered with the sponsor's quadrivalent seasonal influenza vaccine (FLU-D-QIV) in adults ≥ 50 years of age. Subjects were followed for 12 months after second vaccination. The study was conducted between October 2013 and March 2015 in Canada, Germany and the US.

Evaluator commentary: other immunogenicity studies

The dossier contained a number of further studies all of which had immunogenicity, rather than efficacy, endpoints.

In Study ZOSTER-026 two doses of HZ/su in a 0 and 6 month schedule was found to be non-inferior to a 0,2 month schedule, however the 0 and 12 month vaccination interval did not meet the non-inferiority criterion. The sponsor has concluded that the vaccine dosing interval should be 2 months but could be extended to 6 months and a 12 month interval is not recommended. The study was based on humoral immunity despite cell mediated immunity being accepted as the more important response for HZ prevention. As there are currently no correlates of immune protection it is difficult to interpret the findings of the study and so at this stage the evaluator only recommends a 0 and 2 month schedule.

In subjects with a previous history of HZ (Study ZOSTER-033), the humoral immune responses to HZ/su were high and the study met its primary objective as the lower limit (LL) of the 95% CI for the VRR was 82% (≥ 60%). Again, without data on correlates of protection, the interpretation of the results is difficult. The sponsor proposed that the high rate of suspected HZ cases in this study could be due to over reporting by study subjects. The lack of laboratory confirmation of these HZ cases means that no conclusions on this can be drawn.

Study ZOSTER-004 found that concomitant administration of quadrivalent seasonal influenza vaccine (FLU D-QIV) with HZ/su vaccine was acceptable with no immunological interference for either vaccine. It is noted that there are ongoing studies with pneumococcal vaccine (Pneumovax 23) (Study ZOSTER-035) and diphtheria-tetanus-pertussis vaccine (Boostrix) (Study ZOSTER-042). The sponsor has been queried on whether there are plans to assess administration with other adjuvanted vaccines.

Further studies are planned in the immunocompromised patient indication.

For the full details of the evaluation of these studies please see Attachment 2, extract from the clinical evaluation report.

Evaluator's conclusions on efficacy

The efficacy of the HZ/su vaccine was based on two concurrent pivotal Phase III studies; Study ZOSTER-006 and Study ZOSTER-022. These were large scale, randomised, observer blind, placebo controlled, multicentre studies, conducted in 18 countries worldwide. The primary objective of the studies was to evaluate vaccine efficacy compared to placebo in preventing HZ in adults ≥ 50 and ≥ 70 years of age, respectively. Both studies had the same design and subjects were randomised in a 1:1 ratio to receive two doses of HZ/su or saline placebo 0.5 mL via IM injection two months apart. Stratification by age group was undertaken to achieve comparable numbers of HZ cases in the three main age strata (50 to 59 years of age, 60 to 69 years of age, ≥ 70 years of age).

Subjects were excluded if immunosuppressed for any reason. Baseline medical conditions were not described in the clinical study report (CSR) for either study and this was queried. This is important to address comparability between groups and the effects of conditions which may predispose to HZ.

Having the two studies allowed for greater enrolment in older subjects. This separation was undertaken due to the higher PHN incidence in those aged ≥ 70 years and also to accurately assess vaccine efficacy as it was assumed vaccine efficacy may decrease with age. The study design and oversight was appropriate and supported by regulatory advice.

The primary endpoint was HZ as confirmed by polymerase chain reaction (PCR) and all suspected HZ cases were reviewed by a blinded HZ Adjudication Committee. PHN was a secondary endpoint in the individual studies but for those aged ≥ 70 years was a primary endpoint in the pooled analysis of the two studies. Pooling was acceptable due to the studies having the same design, inclusion/exclusion criteria and treatment. Pain assessment was based on the Zoster Brief Pain Inventory (ZBPI) which was completed daily until 28 days post HZ onset and then weekly. PHN was defined as the presence of HZ associated severe 'worst' pain (≥ 3 on the ZBPI questionnaire) persisting or appearing more than 90 days after onset of the HZ rash.

Efficacy analysis was conducted on the modified TVC which excluded subjects who did not receive the second dose of vaccine, who developed confirmed HZ prior to 30 days post second vaccination, or who did not receive vaccine according to the protocol. It was, however, supported by the TVC analysis which included subjects who may have only received one dose of vaccine which is of clinical relevance.

Analysis of Study ZOSTER-006 was undertaken in a two-step procedure, first HZ VE and then at EOS for PHN efficacy, due to earlier case accrual in Study ZOSTER-006. There was a 'Firewall team' set up to maintain study blind between the two analyses.

Statistical analysis description was not completely clear on how multiplicity was controlled and also the impact of futility analyses conducted during the study and this has been questioned.

The studies were terminated early as the required number of cases of HZ and PHN had been met, vaccine efficacy was high and there was a desire to offer vaccine to the placebo group.

There was a site in Mexico with significant GCP non-compliance and its data were excluded from analysis of both studies. The site had included a significant number of subjects: 671 (4.15%) in Study ZOSTER-006 and 865 (5.84%) in Study ZOSTER-022. Overall approximately 5% of enrolled subjects were excluded from TVC analyses in the two studies. The total vaccinated cohort for Studies ZOSTER-006 and ZOSTER-022 was 15,411 and 13,900 subjects, respectively.

For Study ZOSTER-006 there were 14,759 subjects in the mTVC. The median follow up time was 3.1 years at the first HZ analysis and 4.1 years at the end of Study HZ and PHN analysis. For Study ZOSTER-022 the median follow up time was 3.9 years.

The HZ/su vaccine was found to have very high efficacy in both studies. In Study ZOSTER-006, the HZ incidence was 0.3 and 9.1 per 1000 person years in the HZ/su and placebo groups, respectively (6 versus 210 cases). This resulted in a vaccine efficacy of 97.2% (95% CI: 93.7 to 99.0%; $p < 0.0001$) in this population of ≥ 50 year olds. Efficacy was consistent across age groups (50 to 59, 60 to 69, ≥ 70 years of age) and the LL of 95% CI for VE was at least 87%.

In Study ZOSTER-022, the mTVC included 13,163 subjects and the median follow up time was 3.9 years. The HZ incidence was 0.9 and 9.2 per 1000 person years in the HZ/su and placebo groups, respectively (23 versus 223 cases). The HZ VE in the adults aged ≥ 70 years was 89.8% (95% CI: 84.3 to 93.7%, $p < 0.0001$). Efficacy was similar in the two age subgroups (70 to 79 years of age and ≥ 80 years of age). Data from Study ZOSTER-022 was supported by the pooled analysis where VE in the ≥ 70 years of age was 91.3% (95% CI: 86.9 to 94.5%).

In both studies, results were consistent across geographic regions and gender and supported by sensitivity analyses.

There were very few cases of HZ in vaccinated subjects and it would be worthwhile to understand if there were any features in these subjects such as baseline conditions and immunological results that could have explained the breakthrough.

Both studies demonstrated efficacy against PHN: 100% in Study ZOSTER-006 and 85.5% in Study ZOSTER-022. In Study ZOSTER-006 there were no PHN cases in the HZ/su group and 18 in the placebo group. In Study ZOSTER-022, there were 4 and 28 cases in the respective groups, with an incidence of 0.2 and 1.1 per 1000 person-years. In the pooled analysis for those aged 70 years and over, VE against PHN was 88.9% (95% CI: 68.7 to 97.1%). The impact of the definition used for PHN has been questioned. For those with HZ, there was no significant reduction in the incidence of PHN (VE of 0.29%, 95% CI: -161.53% to 65.57%) and so the vaccine efficacy in preventing PHN is likely due to its effect on HZ. The sponsor should comment on whether there could be an increased risk of PHN in those with HZ who had been vaccinated.

The high vaccine efficacy led to a small number of cases in the vaccinated group and therefore assessment of secondary endpoints was difficult.

Post-hoc analysis of pooled data reported high efficacy against HZ related complications other than PHN. This fact has been included in the proposed indication *'prevention of HZ and HZ related complications such as PHN'.* The very limited number of cases, the post-hoc analysis and the varying pathogenesis mean that inclusion of complications other than PHN is not endorsed in the proposed indication. The data may be included in the Clinical Trial section of the PI.

There was a reduction in the use and duration of use of pain medications in Study ZOSTER-022, however there was no reduction in the duration of actual pain and data were not supported by results from Study ZOSTER-006.

Efficacy was demonstrated out to 4 years post vaccination however the issue of possible waning efficacy and the need for booster vaccination has not yet been defined.

Co-administration with quadrivalent seasonal influenza vaccine found no evidence of immunological interference.

A 0 and 6 month vaccination schedule was non-inferior to the 0 and 2 month schedule based on humoral immune response. Nonetheless, due to the lack of correlates of protection and lack of CMI data the 0 and 6 month schedule cannot be supported at this stage. The 0 and 12 month schedule did not meet non-inferiority criteria.

The vaccine was immunogenic in subjects with a prior episode of HZ.

The indication for use in immunocompromised subjects is not the subject of this submission. The two submitted studies in autologous HCT recipients and HIV-infected adults found that three doses of vaccine were immunogenic.[9]

Safety

Studies providing safety data

Pivotal and/or main efficacy studies

In Study ZOSTER-006 and Study ZOSTER-022, solicited AEs were collected in the diary card subset of subjects for seven days from Day 0 to Day 6 after each vaccination. Solicited local (injection site) AEs included pain, redness and swelling. Solicited general AEs included fatigue, fever, GI symptoms (nausea, vomiting, diarrhoea and/or abdominal pain), headache, myalgia and shivering. Daily temperature was also recorded. All other AEs were reported as 'unsolicited' and were collected during the 30 days post vaccination. For subjects not in the diary card subset, local and general symptoms post vaccination were recorded as unsolicited AEs. If there was an unsolicited AE with a medically attended visit this was recorded up to Month 8.

HZ and PHN were not considered an AE or serious adverse event (SAE) although complications of these conditions were. All suspected cases of HZ were confirmed by PCR or the HZ adjudication committee.

AE intensity was graded as follows: 0 being none; 1 mild; 2 moderate; and 3 severe and preventing normal everyday activities. Redness and swelling were scored: 0 < 20 mm; 1 ≥ 20 mm to ≤ 50 mm; 2 > 50 mm to ≤ 100 mm; and 3 > 100 mm diameter. Temperature was scored: 0 < 37.5°C; 1 37.5°C to 38.0°C; 2 38.1°C to 39.0°C; and 3 > 39.0°C (see Table 33, Attachment 2).

SAEs were recorded from Day 0 to Month 14, or to study completion if the SAE related to study participation or if it was fatal. SAEs were also analysed if occurring in the 30 day period post vaccination. Information on potential immune mediated diseases (pIMDs) was collected for the duration of the study.

Other safety/immunogenicity studies

There were 17 further studies, two in immunocompromised adults and 15 in adults ≥ 50 years of age. In this latter group, 6 studies were extension studies.

In all studies solicited and unsolicited AEs were recorded on diary cards, the solicited AEs for 7 days and unsolicited AEs for 30 days post vaccination. SAEs were collected in all studies for their duration from the time of study vaccination. Study EXPLO-CRD-004 had follow up for 42 months and Study ZOSTER-003 for 72 months. Potential immune related diseases (pIMD) were collected for the study duration.

Haematology and biochemistry parameters were assessed in Studies EXPLO-CRD-004, ZOSTER-003, ZOSTER-010 and ZOSTER-023, as well as in immunocompromised (IC) adults in Studies ZOSTER-001 and ZOSTER-015. Suspected cases of HZ were evaluated by PCR or an expert in Studies ZOSTER-001 and ZOSTER-015.

[9] Clarification: While three doses of vaccine were immunogenic, in the 3-dose HZ/su group of ZOSTER-001, the incremental increase in the immune response after the third dose of HZ/su, as compared to the response after 2 doses was modest. The 2 dose schedule was immunogenic in immune compromised subjects.

Data pooling

Safety data from studies in adults ≥ 50 years of age who received the final formulation of vaccine (50 µg gE/ASO1B) in a 0 and 2 month schedule by IM injection, and had at least one year of follow up post vaccination, were pooled. The data were grouped into the 'main safety pooling analysis' where HZ/su was compared to placebo and the studies had similar design (Studies ZOSTER-006 and ZOSTER-022), or the 'broader safety pooling analysis' (see Table 35, Attachment 2).

When there was co-administration (Study ZOSTER-004 with FLU-D-QIV) or assessment in IC adults (Studies ZOSTER-001 and ZOSTER-015) the data were not included in pooled analyses. Data from Studies ZOSTER-007 and ZOSTER-026 were not included in the safety pooling as one year follow up was not available at the time of database lock. Study EXPLO-CRD-004 was not included as follow up was for 10 months and the extension Studies ZOSTER-018 and ZOSTER-019 only recorded study related SAEs and suspected HZ cases. Study ZOSTER-023 in Japanese ethnic origin subjects which only had 6 months of follow up and Studies ZOSTER-001 and ZOSTER-015 which were in immunocompromised (IC) adults were also not included.

Patient exposure

The total exposure to HZ/su in the clinical development program studies included in the dossier was 17,204 subjects. The breakdown of how studies were included in the safety pools is shown in Figure 12, Attachment 2. In the main safety pool (Studies ZOSTER-006 and ZOSTER-022), there were 14,745 subjects who received at least one dose of HZ/su vaccine (Table 36, Attachment 2). In the broader safety pool, there were 15,493 adults ≥ 50 years of age who received at least one dose of HZ/su vaccine and 9,078 who were ≥ 70 years of age. Approximately 95% of subjects received two doses of vaccine. Exposure in studies not included in the broader safety pool is summarised in Table 37 of Attachment 2. In the main safety pool there were 14,660 subjects who received placebo.

Safety issues with the potential for major regulatory impact

Potential Immune Mediated Diseases

Main safety pool

There were 179 (1.2%, 95% CI: 1.1 to 1.4) and 202 (1.4%, 95% CI: 1.2 to 1.6) subjects in the HZ/su and placebo groups, respectively, with a potential immune mediated disease (pIMD). The most frequent conditions were polymyalgia rheumatica (32 versus 29 subjects respectively), rheumatoid arthritis (20 versus 26 subjects), psoriasis (15 versus 18 subjects) and autoimmune thyroiditis (13 versus 10 subjects). The rate of pIMDs with an onset from the first vaccination to 30 days post last vaccination was 0.2% in each group, and in the period up to 1 year post last vaccination was 0.6% and 0.7%, respectively. The remainder (about half the cases of pIMDs in each group) had an onset over 1 year post vaccination.

Treatment related pIMDs were reported in 0.1% of each treatment group. There were no notable differences in the rate of pIMDs by age group (1.2% versus 1.4% in 50 to 69 years of age and 1.3% in both groups in ≥ 70 years of age).

There was no evident imbalance in the occurrence of pIMDs between the vaccine and placebo groups.

Broader safety pool

In the broader safety pool, the rate of pIMDs during the whole follow up period was 1.2%. There were five additional subjects with a pIMD and none were considered treatment related.

Hypersensitivity

Main safety pool

Using the Standardised MedDRA Query (SMQ) 'hypersensitivity narrow', the rate of such AEs was 2.6% and 2.4% in the HZ/su and placebo groups, respectively, and the rate per dose was 1.4% and 1.3%. The most frequent preferred terms were rash, injection site rash, eczema, urticaria and dermatitis. Using the SMQ 'anaphylactic reaction narrow' in the 30 day post vaccination period, there was a single case identified in the HZ/su group. This occurred after Dose 1 and was graded level 1. The subject had site pain, pyrexia, fatigue, injection site redness, chills, nausea and disorientation and recovered by Day 3 without treatment.

Broader safety pool

The rate of 'hypersensitivity' SMQ was 2.5% and was reported after 1.4% of doses. There were no additional anaphylaxis cases in the broader safety pool.

Other studies

No cases of anaphylaxis were identified.

Laboratory tests

Laboratory assessments were undertaken in Studies EXPLO-CRD-004, ZOSTER-003, ZOSTER-010 and ZOSTER-023. There were no evident safety signals reported.

Vital signs and clinical examination findings

There was no routine vital sign measurement during the studies apart from body temperature which was ascertained prior to each vaccination. Clinical examination was performed at study entry if indicated from the medical history. Clinically significant abnormalities during the study were reported as AEs as appropriate.

Safety in special populations

Immunocompromised

Studies ZOSTER-001 and ZOSTER-015 assessed the vaccine in adults ≥ 18 years of age who had received an autologous haematopoietic stem cell transplant (HCT) and or who had HIV infection, respectively. In Study ZOSTER-001, vaccine was tolerated with no evident safety signals apart from an increase in symptoms following 3 doses compared to two doses. There were 9 deaths, 7 from underlying malignancy and two of unknown cause. Of the 33 subjects with an SAE, one (pneumonia in HZ/su group) was considered treatment related. There were no pIMDs and two cases of suspected HZ.

In HIV infected adults, three doses of vaccine (0,2, 6 months) were tolerated. There were no deaths and there were six (8.1%) SAEs in the HZ/su and 2 (4.1%) in the placebo group. There was one withdrawal in HZ/su group from portal hypertension and oesophageal varices haemorrhage. There were no pIMDs and one case of HZ in the HZ/su group. The study was put on hold once to review 4 cases of protocol-defined worsening of the underlying HIV. The study was continued when the review committee found no particular safety concern.

The clinical development program in this indication is ongoing and this indication does not form part of this application.

The sponsor reported in the Clinical Overview that the Independent Data Monitoring Committees (IDMC) overseeing the three ongoing studies in this indication have not reported any safety concerns.

Previous HZ

In the open label, non-randomised Study ZOSTER-033, 77.9% of subjects with a history of HZ reported solicited local symptoms and 71.6% reported solicited general symptoms. Grade 3 pain was reported following 4.4% of doses by 8.4% of subjects and Grade 3 fatigue following 6.1% of doses by 10.5% of subjects. There were no evident safety signals.

Japanese ethnicity

In the small Phase I Study ZOSTER-023 in adults with Japanese ethnic origin, the vaccine was tolerated however the numbers were too small to draw conclusions (10 subjects aged 50 to 69 years).

Younger adults

Data on younger adults aged 18 to 30 are available from the two early phase studies: Studies EXPLO-CRD-004 and ZOSTER-023. There were no evident safety signals from these small studies.

Pregnancy and lactation

There are no data on the use of vaccine in pregnant or lactating women.

Safety related to drug-drug interactions and other interactions

In Study ZOSTER-004, co-administration of HZ/su with FLU-D-QIV was assessed. The rate per dose of solicited local symptoms was higher in the group that received co-administered vaccine compared the control group who received vaccine doses alone (77.1% versus 57.4%). In particular, there was a higher rate of pain (73.6% versus 54.2%) and Grade 3 pain (8.4% versus 4.4%). Solicited general symptoms were also more frequent in the co-administered group (62.5% versus 49.7% overall per dose). There were no notable differences in the rate of unsolicited AEs following each vaccine dose (15.5% versus 17.0%).

Post-marketing data

Not applicable.

Evaluator's conclusions on safety

The total exposure to HZ/su in the studies included in the dossier was 17,204 subjects. The main safety pool, which contained data from the two pivotal Phase III studies, included 14,745 adults ≥ 50 years of age who received at least one dose of HZ/su vaccine. Of these, approximately 95% received two doses of vaccine. The mean follow up period was 3 years.

The HZ/su vaccine was reactogenic with a high rate (overall rate per dose) of local symptoms of pain (68%), redness (38%) and swelling (26%) as well as of general symptoms of myalgia (33%), fatigue (32%) and headache (26%). Other common symptoms were GI disorders (nausea, vomiting, diarrhoea and/or abdominal pain) (10.7%), shivering (17.6%) and fever (12.8%).

Most reactions were Grade 1 or 2 and symptoms tended to last less than 4 days. Severe, Grade 3, local symptoms were reported in ≤ 6.4% of subjects (pain being the most frequent) and Grade 3 general symptoms in ≤ 5.3% (fatigue and myalgia the most frequent). It was noted that the rate of Grade 3 general symptoms increased with the second dose of HZ/su (5.7% to 8.0%).

The safety data indicate that local and general solicited symptoms rate tends to be higher in 50 to 69 years of age group than the ≥ 70 years of age subjects.

The death rate in the study was comparable between HZ/su and placebo groups (4.3% versus 4.6%) and rates were also similar in the two age groups (50 to 69 and ≥ 70 years of age). Only one death was deemed treatment related by an investigator (neutropaenic sepsis in a 90 year old subject with acute myeloid leukaemia (AML) diagnosed 75 days post vaccination). The sponsor has been asked to comment on any other such malignancies.

The rate of SAEs (fatal and non-fatal) was similar between groups in the main safety pool (12.8% versus 13.3%, risk ratio (RR) = 0.97 (95% CI: 0.91 to 1.03) unadjusted p = 0.316) and there were no evident safety signals. Rates were similar between treatment groups in the two main age groups.

In the briefing document to the Vaccines and Related Products Advisory Committee of the FDA (13 September 2017 meeting) imbalances in a number of conditions were noted including optic ischaemic neuropathy, temporal arteritis, amyotrophic lateral sclerosis, osteonecrosis and convulsions. It was also noted in the EU regulatory evaluation that the sponsor has been asked to comment on whether the adjuvanted vaccine has shown any evidence of impact on the immune system that may increase the risk of infections or malignancy. Apart from the finding on ovarian cancer (0.05% versus 0%), there were no evident signals on SAE rates. Nonetheless, further discussion on these points from the sponsor has been requested.

Data on medically attended visits were stated to have been collected to Month 8; however pooled data on associated adverse events could not be located. The sponsor has been asked to discuss these events and comment on any imbalances between the treatment groups.

During the whole follow up period the withdrawal rate due to non-serious AEs was 0.5% versus 0.2% and due to an SAE was 4.7% versus 4.9%. There was a slightly higher withdrawal rate for non-serious AEs in the period up to one month post the second vaccine dose (0.4% versus 0.1%). This may be due to the vaccine's reactogenicity. The sponsor has been asked to comment on the type of adverse events leading to premature discontinuation.

There were no notable differences between the HZ/su and placebo groups in the rates of pIMDs in the main safety pool (1.2% versus 1.4%) and about half the events were reported over one year post vaccination. Such events are rare and despite the sample size of about 15,000 there may be insufficient data to adequately detect such a risk. Pharmacovigilance surveillance will therefore be crucial.

There was one report of 'anaphylaxis' which did not require treatment and no increased rate of hypersensitivity reactions. There were also no clinically relevant changes in laboratory parameters in the studies where these were assessed.

In the small number of adults with history of HZ, the vaccine was tolerated with no evident safety concerns although there was no control group in the study. The product development in the immunocompromised population is ongoing and to date in the limited population of autologous HCT recipients and HIV infected subjects no safety concerns were evident. Background medical history was not discussed and, while subjects with immunosuppression were excluded, the safety in elderly patients with pre-existing immune mediated disorders should be further outlined.

There are no data in pregnant or lactating women and data in adults under 50 years of age are limited. There are no data as yet on the need for or safety of a booster dose of vaccine.

HZ/su given with quadrivalent seasonal influenza vaccine increased local and general solicited symptom rates and it is recommended that this is noted in the PI.

Subcutaneous vaccination leads to an increased rate of local reactions and should not be undertaken.

First round benefit-risk assessment

First round assessment of benefits

Table 6, shown below, summarises the benefits of Shingrix recombinant varicella zoster virus glycoprotein E antigen (vaccine) for the proposed usage, as evaluated at the first round.

Table 6: First round assessment of benefits

Benefits	Strengths and Uncertainties
High efficacy against HZ in adults ≥ 50 years VE of 97.2% (95% CI: 93.7-99.0%).	Strong and robust evidence from a well-designed and powered study with a clear, well documented endpoint. Results were consistent across subgroups and sensitivity analyses.
High efficacy against HZ in adults ≥ 70 years VE of 91.3% (95% CI: 86.9-94.5%)	Strong and robust evidence from well designed and powered studies with a clear, well documented endpoint. This was the primary prespecified endpoint of the pooled study analysis and was supported by results in the two individual studies.
High vaccine efficacy against HZ across all age groups (50 to 59, 60 to 69, 70 to 79 and ≥ 80 years of age).	The secondary endpoint data were consistent and supported by the pooled data for the ≥ 70 years of age group which improved the power of results.
High vaccine efficacy against PHN: ≥ 50 years of age: 100% (95% CI: 77.1 to 100.0%) ≥ 70 years of age: 88.8% (95% CI: 68.7 to 97.1%)	Study ZOSTER-006 in ≥ 50 years of age subjects was not powered for the PHN secondary endpoint, however in the ≥ 70 years of age group PHN was the primary endpoint in the pooled analysis and this result is robust.
No major safety signals	The safety dataset included a broad population of 17,000 exposed subjects with a median follow up time of at least 3 years. From this there was no increased risk of death, SAEs or pIMDs.
Non-live vaccine	There is a potential benefit to patients who cannot be given live vaccination. Initial data in the immunocompromised population appear positive but development is still ongoing.

First round assessment of risks

Table 7, shown below, summarises the risks of Shingrix recombinant varicella zoster virus glycoprotein E antigen (vaccine) for the proposed usage, as evaluated at the first round.

Table 7: First round assessment of risks

Risks	Strengths and Uncertainties
Notable increase in risk of solicited local and systemic symptoms in the week post vaccination.	Robust safety data obtained from the two pooled placebo controlled studies with thorough safety data collection. The diary card subset included 9,764 subjects.
Some increase in reactogenicity (mainly Grade 3 systemic events) with the second dose of vaccine which may lead to decreased compliance with second dose.	Robust safety data obtained from the placebo controlled studies with thorough safety data collection. Effects on compliance are unknown.
Reactogenicity higher in adults aged 50 to 69 compared to those over 70 years.	Robust safety data obtained from the placebo controlled studies with thorough safety data collection. Resultant effects on compliance are unknown.
No immunological correlates of protection.	Supportive studies were based on immunological endpoints. Drawing conclusions on resultant efficacy is therefore difficult, particularly for humoral immunity endpoints. This is relevant for data on a dosing schedule other than 0,2 months.
No data on long term (> 4 years) protection and the need for booster dose has not been determined.	Pivotal studies provided efficacy data to 4 years. There are no data at present on the need for booster dosing. Long term follow up is planned for Studies ZOSTER-006, ZOSTER-022 and ZOSTER-003.
Risk of very rare events is not currently quantifiable.	Detection of rare events was limited by the dataset size to 1/17,000.
Unknown risks in those with pre-existing immune conditions.	Limited data at present in immunocompromised subjects who were excluded from the pivotal studies. The non-live vaccine has a clear clinical place if safe and efficacious in this population.

First round assessment of benefit-risk balance

Herpes zoster and its complications, in particular post herpetic neuralgia, can cause considerable morbidity and current treatment with antiviral therapy is not curative. Consequently, there is a clear clinical place for an efficacious vaccine which can prevent these conditions.

The proposed vaccine, Shingrix, demonstrated in the pivotal studies a high efficacy against herpes zoster of about 97% in adults 50 years and older and importantly a high efficacy against herpes zoster of about 91% in those aged 70 years and older. The currently available zoster vaccine, Zostavax, has a lower reported efficacy particularly in those aged ≥ 70 years who may be most at risk. While there are no head-to-head comparisons, the efficacy results in this dossier for Shingrix are compelling.

Although the study was not powered for this endpoint, Shingrix demonstrated efficacy against post herpetic neuralgia of 100% in those aged ≥ 50 years of age. From pre-specified pooled data analysis, the efficacy against PHN in those aged 70 years and older was robustly demonstrated at approximately 88%. In adults 50 years and over, the efficacy against PHN in those with confirmed HZ was not demonstrated (VE of 0.29%) and, while this may be a result of the very small sample size leading to inadequate power, it is recommended that this potential risk be monitored post-marketing. As there was no decreased risk of PHN in those with confirmed HZ, it is concluded that the vaccine efficacy in preventing PHN is very likely due the effect against HZ.

The vaccine was noted to have high reactogenicity with local injection site reactions and general symptoms such fatigue, headache and myalgia. It is possible that in the clinical practice setting, this reactogenicity could interfere with second dose compliance. As the reactions subsided in a couple of days and are to some extent treatable, it is anticipated that this risk should be manageable. It is recommended that the vaccine's reactogenicity be further outlined in the PI.

There were no major safety concerns although the database size of some 15,000 recipients limits its ability to detect very rare conditions. The risk of hypersensitivity is consistent with other vaccines. There was no increased rate of potential immune mediated disorders after a median safety follow period of about 3 years that should be sufficient to capture events. Nevertheless pharmacovigilance surveillance of such conditions will be important.

The background morbidity of the trial population was not discussed and so has been questioned. This will be necessary to ensure the trial population represents the elderly population in Australia who would receive the vaccine and to determine if there are any safety data on subjects with immune mediated disorders. The vaccine has high immunogenicity and this might impact on the elderly population with pIMDs. This should be discussed and consideration given to conducting further efficacy and safety studies in this population. In the interim, it is recommended to include precautionary wording in the PI and implement pharmacovigilance monitoring.

The product development in the immunocompromised population is ongoing and to date in the limited population of autologous HCT recipients and HIV infected subjects no safety concerns were evident. Zostavax is a live attenuated vaccine and so is contraindicated in immunocompromised patients. Should favourable efficacy and safety data become available, Shingrix, being a non-live vaccine will have an obvious clinical place for immunocompromised subjects.

There are several areas where data are limited or lacking. These include:

- the effect of giving the vaccine to VZV naïve adults
- data on immunological correlates of protection
- co-administration with pneumococcal vaccine and co-administration with other adjuvanted vaccines
- ability to give to adults who have received Zostavax
- the duration of protection beyond 4 to 6 years and the need for booster vaccination
- evidence in the immunocompromised population.

These issues have been covered by conduct of further studies, appropriate wording in the PI or questions (see below).

In summary, an efficacious and safe vaccine against HZ and PHN has an evident clinical place for morbidity prevention. Shingrix was found to have high efficacy against herpes zoster, and consequently its complication of post herpetic neuralgia, across the adult population aged 50 years and older. The vaccine was notably reactogenic, however such effects should be manageable and there were no evident major safety signals or concerns in the data presented.

The vaccination schedule assessed in the efficacy trials was 0 and 2 months. Based on the findings of an immunogenicity study, it has been proposed to allow the period between doses to extend to 6 months. This recommendation was based on humoral immunogenicity data rather than the more relevant cell mediated immune responses. As there are no correlates of protection nor specific efficacy data on the 0 and 6 month schedule, the evaluator does not endorse a schedule other than 0 and 2 months.

The proposed indication includes the prevention of HZ related complications other than PHN. The data on complications other than PHN were very limited and based on post-hoc analyses. As such, the evaluator does not support its inclusion in the indication.

Hence, the benefit-risk balance of Shingrix is unfavourable for the proposed usage, but would become favourable if the changes recommended are adopted and the questions are satisfactorily answered.

First round recommendation regarding authorisation

Approval of Shingrix is not recommended for the following proposed indication:

> *Shingrix is indicated for the prevention of herpes zoster (HZ) and HZ related complications, such as post herpetic neuralgia (PHN), in adults 50 years of age or older.*

Approval is recommended for a revised indication which removes HZ related complications other than PHN. A suggestion is as follows:

> *Shingrix is indicated for the prevention of herpes zoster and post herpetic neuralgia in adults 50 years of age or older.*

This recommendation is subject to satisfactory responses to the questions and the comments on the draft PI and CMI.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

Following evaluation of clinical data provided in response to the first round evaluation, there are no changes to the benefits of Shingrix in the proposed usage as listed the first round assessment of benefits.

Second round assessment of risks

The clinical data provided in response to the first round evaluation included data on immunological correlates of protection. These data indicated a correlation between the gE ELISA antibody level and the protection against HZ in adults ≥ 50 years of age. Consequently, the immunological data from the dosing schedule Study ZOSTER-026 is more clinically relevant.

Apart from this, there are no other changes to the risks of Shingrix in the proposed usage as listed in the first round assessment of risks.

Second round assessment of benefit-risk balance

Following the first round evaluation, the sponsor has satisfactorily answered most questions. Further clinical data was presented and relevant findings include:

- No evident features, clinically or immunologically, in subjects with breakthrough HZ.
- Efficacy against PHN was maintained across differing definitions of PHN pain duration.
- Efficacy against HZ was maintained over 4 years, although maintenance of efficacy against PHN could not be determined due to low case numbers.
- No notable safety signals when medically attended visits up to Month 8 were analysed or when AEs leading to vaccine discontinuation or study withdrawal were assessed.
- Data did not indicate an increased risk of serious infections or neoplasms.
- Baseline morbidity in the trial population was balanced between treatment groups and vaccine efficacy was consistently high across the main disease subgroups assessed.
- In subjects with a pre-existing pIMD, there was no increased rate of exacerbation or of a new onset pIMD. There was a possible increase risk of gout post vaccination.

As previously discussed, pharmacovigilance surveillance of pIMDs will be important and safety assessment in frail elderly adults and in those with immune mediated disorders should be examined in further studies.

The data presented on immunological correlates of protection indicated a correlation between the gE ELISA antibody level and the protection against HZ in adults ≥ 50 years of age. Following on from this, as non-inferiority of the humoral immune response with the 0 and 6 month dosing schedule was demonstrated to the 0 and 2 month schedule in Study ZOSTER-026, it is agreed that the dosing interval may be extended to a maximum of 6 months. As mentioned by the sponsor, the data presented on correlates of protection can only be applied to the population studied and with this particular vaccine and using the sponsor's proprietary testing.

The indication has been satisfactorily reworded and HZ related complications other than PHN have been deleted.

There still remain several areas where data are limited or lacking. These include:

- co-administration with pneumococcal vaccine and or with other adjuvanted vaccines
- ability to give to adults who have received Zostavax
- the duration of protection beyond 4 years and the need for booster vaccination
- efficacy and safety in immunocompromised patients.

These issues have been covered by planned studies and appropriate wording in the draft PI.

The PI has been updated taking into account the majority of comments made after the first round evaluation. There remain a few points to be addressed.

In conclusion, following the second round evaluation the benefit-risk balance of Shingrix is favourable for revised proposed usage.

Second round recommendation regarding authorisation

Approval of Shingrix is recommended for a revised indication:

> *Shingrix is indicated for the prevention of herpes zoster and post herpetic neuralgia in adults 50 years of age or older*.

This recommendation is subject to satisfactory responses to the remaining points on the draft PI.

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[10]

- The sponsor submitted EU-RMP version 0.0 (date 17 October 2016; data lock point (DLP) 12 October 2015) and ASA version 1.0 (April 2017) in support of this application. At the second round, the sponsor submitted an updated EU-RMP version 0.3 (dated 19 December 2017; DLP 12 October 2015).
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below, with changes made in the second round evaluation in bold italics (additions) and strikethrough (deletion).

Table 8: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Nil				
Important potential risks	~~Risk of hypersensitivity reactions (including anaphylaxis)~~	~~ü~~		~~ü~~	

[10] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Risk of potential Immune Mediated Disorders (pMIDs) ***following vaccination***	ü	ü	–	–
Missing information	Long-term efficacy and assessment of the need for additional doses in adults 50 years of age and older.	ü	ü	–	–
	Long-term immunogenicity in adults 50 years of age and older.	ü	ü	–	–
	Use of vaccine in frail adults 50 years of age or older	***ü***	***ü***	***ü***	–
	Use of vaccine in immunocompromised adults	***ü***	***ü***	–	–
	Use of vaccine in adults with pre-existing pIMD	***ü***	***ü***	–	–
	Use of vaccine in adults 50 years of age or older with a history of HZ	***ü***	***ü***	***ü***	–
	Effectiveness of vaccine in preventing HZ, PHN and HZ related complications	***ü***	***ü***	–	–

- Additional pharmacovigilance is underway, in the form of enhanced surveillance, long term extensions (to 10 years) and retrospective analysis of earlier clinical trials, and nine new studies. The studies in immunocompromised adults involve haematopoietic cell transplant recipients, and patients with a haematological malignancy, a renal transplant or a solid tumour treated with chemotherapy.
  - Additional pharmacovigilance studies that are subject to feasibility assessments are a study on immunogenicity, reactogenicity and safety in adults with pre-existing pIMDs, and also an observational study in the US to estimate effectiveness in preventing HZ, PHN and HZ related complications.
- Routine risk minimisation has been proposed by the sponsor to mitigate two areas of missing information (use in frail adults, and use in adults with a history of HZ).

New and outstanding recommendations from second round evaluation

The recommendations made in the first round evaluation, along with consideration of the sponsor's response.

- Recommendation 14. (New recommendation) It is recommended to the delegate that the PI include a precaution statement such as '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' as routine risk minimisation for the safety concerns for the two groups mentioned.
- Recommendation 15. When available a revised EU-RMP that considers the outcome of each pharmacovigilance study should be submitted to the TGA for review.

- Recommendation 16. When available an updated ASA that considers the changes made to the EU-RMP (final approved version) should be submitted to the TGA for review. The updated ASA should address the generalisability of the pharmacovigilance studies to the Australian population.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> The Shingrix EU-Risk Management Plan (RMP) (version 0.3, dated 19 December 2017, data lock point 12 October 2015), with Australian Specific Annex (version 1, dated April 2017), included with submission PM-2017-01784-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the PSUR requirement:

> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

As Shingrix is a new biological entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> 'Shingrix (recombinant varicella zoster virus glycoprotein E antigen) is to be included in the Black Triangle Scheme. The PI and CMI for Shingrix must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Other advice to the Delegate

The attention of the Delegate is drawn to the following matters.

The sponsor has advised that it does not agree to the addition of a statement referring to 'official guidelines' within the indication section of the PI. The sponsor advises that its position has previously been discussed with the TGA for other vaccines. The sponsor's view is that the indication should be based only on data it holds, and notes that the Australian Immunisation Handbook or other official guidelines are outside the control of the sponsor and could potentially recommend use of the vaccine for populations for which the sponsor does not hold data.

The sponsor has advised that it does not agree to the inclusion in the PI of information on pIMDs as adverse events. Comparable regulatory authorities (the FDA and Health Canada)

have included brief information on pIMDs in the adverse events section of the prescribing information.

From the enhanced pharmacovigilance undertaken to date on pIMDs, the sponsor has identified gout as one of the 14 disorders to be further characterised in the target population. The US prescribing information specifically mentions gout as an unsolicited adverse event.

The PI does not mention that the vaccine provides an unknown duration of protection.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Introduction

This is a submission seeking registration of a new vaccine Shingrix. Shingrix is a non-live subunit vaccine consisting of 50µg of the recombinant subunit varicella zoster virus (VZV) glycoprotein E (gE) antigen and the $AS01_B$ adjuvant system. The gE antigen is produced by recombinant DNA technology in CHO cells. $AS01_B$ is a new adjuvant that is not included in any licensed vaccine. Shingrix will be available as a powder and suspension liquid to be made into a suspension for injection. The active substance of Shingrix is varicella zoster virus glycoprotein E antigen (VZV gE) (ATC code: J07BK03). In Shingrix, VZV gE is combined with an adjuvant ($AS01_B$), and is designed to induce antigen specific cellular and humoral immune responses in individuals with pre-existing immunity against varicella zoster virus. In this Overview, the herpes zoster vaccine is referred to as HZ/su and in early studies as gE/$AS01_B$.

Overseas regulatory status

The sponsor stated that the application submitted to the TGA is based on the same data provided to the EU, USA and Canada. The vaccine has now been approved by the FDA, Health Canada, and the EMA (28 March 2018) and in Japan (23 March 2018). For details see Table 1, above.

Quality

The quality evaluations consist of the following aspects: primary evaluation, infectious disease/viral safety, container safety, microbiology (sterility) and endotoxins.

All the above evaluations are completed. There are no outstanding quality issues in regards to approval of Shingrix. Conditions of registration from quality aspects were provided.

Nonclinical

The nonclinical data provided are satisfactory. The primary pharmacology studies adequately demonstrated sero-conversion of animals to virus antigen present in the vaccine tested in presence of the $AS01_B$ adjuvant. However, due to the limitation of an adequate animal model to determine the efficacy of the vaccine, protection against HZ would need to be established by clinical studies.

There were adequate repeat dose toxicity and local tolerance studies with Shingrix and the adjuvant did not raise safety issues. Studies in rats and rabbits showed no reproductive toxicity. An Australian Pregnancy Category B2 is recommended.[5]

There are no nonclinical objections to the vaccine registration provided protection against HZ is demonstrated by clinical data.

Clinical

The clinical dossier included data from 19 clinical studies. There were two pivotal efficacy studies, Studies ZOSTER-006 and ZOSTER-022. Other studies provided immunogenicity but no efficacy data.

The 19 clinical studies included are as follows:

- Phase I studies:
  - Study EXPLO-CRD-004 - Phase I/II exploratory study with varicella vaccine
  - Study ZOSTER-018, -019 - Phase I/II extension studies of Study EXPLO-CRD-004
  - Study ZOSTER-023 - Phase I study in adults of Japanese ethnic origin
- Phase II studies:
  - Study ZOSTER-003 - antigen dose selection study
  - Study ZOSTER-011, -012, -013 - extension studies of Study ZOSTER-003 for years 1, 2 and 3
  - Study ZOSTER-024 - extension study of Study ZOSTER-003 to year 6
  - Study ZOSTER-010 - adjuvant dose selection study
- Phase III studies in healthy adults
  - Study ZOSTER-006 - pivotal efficacy and safety in ≥ 50 year olds
  - Study ZOSTER-022 - pivotal efficacy and safety in ≥ 70 year olds
  - Study ZOSTER-004 - co-administration with influenza vaccine
  - Study ZOSTER-007 - lot-to-lot consistency study
  - Study ZOSTER-026 - schedule comparison study
  - Study ZOSTER-032 - route of administration study (SC versus IM)
  - Study ZOSTER 033 - adults with previous HZ
- Phase I/II in immunocompromised adults
  - Study ZOSTER-001 - autologous haematopoietic stem cell transplant recipients
  - Study ZOSTER-015 - HIV infected adults

The detailed evaluation of those studies can be found in the CER while a brief discussion of some studies is included in this Overview.

Studies relating to selection of dose, dosing schedule, and administration route

Study ZOSTER-003

Similar CMI responses and reactogenicity were found with the 50 µg and 100µg antigen doses. The 25 µg dose was inferior to the higher doses in terms of CMI response. Therefore the 50 µg was selected for further development.

Study ZOSTER-010

The presence of $AS01_B$ adjuvant resulted in a superior immune response but also increased reactogenicity. The full dose $AS01_B$ resulted in an increased immune response (CMI and humoral) compared to half strength dose and was selected for further development.

Study ZOSTER-026

An open label, randomised, parallel group immunogenicity study, assessed two vaccination intervals longer than 2 months (0 and 6 months; and 0 and 12 months) in 354 adults ≥ 50 years of age. As measured by the anti-gE antibody GMC ratio one month post second vaccination, the 0 and 6 month schedule was found to be non-inferior to the 0 and2 month schedule, however the 0,12 month vaccination interval did not meet the non-inferiority criterion (GMC ratio UL of the 97.5% CI < 1.5).

Nonetheless, due to the lack of correlates of protection and lack of CMI data, the 0 and 6 month schedule is not supported by the clinical evaluator. The 0 and 12 month schedule did not meet non-inferiority criteria.

StudyZOSTER-032

Subcutaneous administration was associated with high local reactogenicity and development was ceased. IM route was selected.

Based on the above data, the clinical evaluator considers the selected dosing schedule/ route for use in Phase III program are justified: two doses of HZ/su, IM injection, two months apart.

Efficacy

Pivotal studies assessing vaccine efficacy

The assessment of VE was based on two pivotal Phase III studies: Studies ZOSTER-006 and ZOSTER-022. These were large scale, randomised, observer blind, placebo controlled, multicentre studies. The primary objective of the studies was to evaluate VE compared to placebo in preventing HZ in adults ≥ 50 and ≥ 70 years of age, respectively. Both studies had the same design and subjects were randomised to receive two doses of IM Shingrix (HZ/su) or saline placebo two months apart. Stratification by age was undertaken to achieve comparable numbers of HZ cases in the three main age strata (50 to 59 years of age, 60 to 69 years of age, ≥ 70 years of age).

Eligibility criteria for enrolment were detailed in the CER. It is noted that the studies excluded, among other, subjects who were immunocompromised, had a history of prior HZ, and had prior vaccination against HZ or varicella. The primary endpoint of the two studies was incidence of HZ cases (confirmed by PCR) in the modified Total Vaccinated Cohort (mTVC). All suspected HZ cases were reviewed by a blinded HZ Adjudication Committee. Incidence of PHN was a secondary endpoint in the individual studies but for those aged ≥ 70 years was a primary endpoint in the pooled analysis of the two studies.

Efficacy analysis was conducted on the mTVC which excluded subjects who did not receive the 2nd dose of vaccine, who developed confirmed HZ prior to 30 days post second vaccination, or who did not receive vaccine according to the protocol. It was, however, supported by the TVC analysis which included subjects who may have only received one dose of vaccine which is of clinical relevance.

Vaccine efficacy against Herpes Zoster (primary efficacy outcome)

Study ZOSTER-006

There were 14,759 subjects in the mTVC. The median follow up time was 3.1 years at the first HZ analysis and 4.1 years at the end of study HZ and PHN analysis. In the mTVC, there were 6 cases of confirmed HZ in the HZ/su group and 210 in the placebo group. Confirmation of HZ by PCR was determined in 4 of the 6 cases in the HZ/su group and 189/210 of the placebo group. The overall HZ incidence per 1000 person-years was 0.3 and 9.1 in the HZ/su and placebo groups, respectively. This resulted in a VE of 97.2% (95% CI: 93.7 to 99.0%; $p < 0.0001$) in ≥ 50 year olds, and therefore the study met its primary objective as the LL of the 95% CI was > 25%. VE was consistent across the age groups: 96.57% in 50 to 59 years of age, 97.36% in 60 to 69 years of age and 97.93% in ≥ 70 years of age. As the LL of the 95% CI for VE in the 50 to 59 and 60 to 69 year age groups was > 10% the study met its secondary objectives. At end of study, after a mean follow up of 3.9 years, there were a further 47 cases of HZ (3 and 44 in the HZ/su and placebo groups, respectively). At this point, the incidence of HZ was 0.3 and 8.9 per 1000 person years, respectively and VE was 96.50% (95% CI: 93.2 to 98.5%). VE was consistent between males and females across the age groups and also across geographical regions. Sensitivity analysis using Cox regression found similar results with VE > 96% overall and across the age groups.

Study ZOSTER-022

The mTVC included 13,163 subjects. After a median follow up of 3.9 and 3.7 years in the HZ/su and placebo groups, respectively, there were 246 subjects with a confirmed HZ episode (23 in the HZ/su group and 223 in the placebo group). The incidence rate was 0.9 and 9.2 per 1000 person-years, respectively. This resulted in a HZ VE of 89.79% (95% CI: 84.29 to 93.66%, $p < 0.0001$). As the LL of the 95% CI was above 10%, the study met its primary objective. HZ VE in the 70 to 79 years of age group was 90.02% and in the ≥ 80 years of age group was 89.08%. Results were consistent between males and females and across geographic regions. Analysis of VE over the study period found HZ VE in the 4th year of 85.1% (95% CI: 64.5 to 94.8%). Analyses of VE in the TVC and the ATP populations were also consistent with the mTVC.

Vaccine Efficacy against PHN (secondary efficacy outcome)

Study ZOSTER-006

Considering all subjects (independent of the occurrence of HZ), there were no PHN cases in the HZ/su group and 18 in the placebo group, so the VE against PHN is 100%.

Study ZOSTER-022

Considering all subjects (independent of the occurrence of HZ), there were 4 and 28 cases in the HZ/su and placebo group respectively, with an incidence of 0.2 and 1.1 per 1000 person-years. The VE against PHN is 85.5%.

Other secondary objectives

Other secondary objectives, such as VE in reducing the HZ related mortality and hospitalizations, the incidence of HZ associated complications (other than PHN), and the use of pain medications for HZ, were evaluated in subjects with confirmed HZ in the individual ZOSTER-006 and ZOSTER-022 studies. As a consequence of the high VE against HZ, a low number of breakthrough cases were accrued, and therefore it was not possible to draw firm conclusions on VE against HZ related complications, on VE in reduction of confirmed HZ episode related mortality and hospitalizations. There were no HZ related mortality cases in the two pivotal studies and there were 5 HZ related hospitalizations in the placebo group in Study ZOSTER-022. Only a few HZ complications were reported: no cases in HZ/su group in Study ZOSTER-006 and one case of ophthalmic disease in HZ/su

group in Study ZOSTER-022 compared to 6 and 10 HZ related complications in the Placebo group of Studies ZOSTER-006 and ZOSTER-022, respectively.

In Study ZOSTER-022, when considering the reduction of the use of pain medication in adults ≥ 70 years of age with confirmed HZ, VE was 39.60% (95% CI: 10.79 to 64.75), with 43.5% of subjects in the HZ/su group and 71.8% of subjects in the Placebo group having taken at least one pain medication for HZ. VE in terms of reduction of duration of pain medication associated with HZ was 49.25% (95% CI: 2.92 to 73.47), with a median duration of pain medication of 30 days in the HZ/su group and 38 days in the Placebo group. Note that in Study ZOSTER-006, the significant reduction of use and duration of pain medication was not shown in ≥ 70 years of age, and neither overall nor in the other age strata, as a consequence of the high HZ VE and subsequently low number of HZ cases in the HZ/su group.

Pooled analysis of Studies ZOSTER-006 and ZOSTER-022

Pooling was considered acceptable as the two studies having the same design, inclusion and exclusion criteria and treatment. PHN was defined as the presence of HZ associated severe 'worst' pain persisting or appearing more than 90 days after onset of the HZ rash. The TVC included 29,305 subjects with 14,645 and 14,660 in the HZ/su and placebo groups, respectively. The mTVC included 27,916 (95.3%) subjects and the ATP cohort 25,786 (88.0%). In the TVC, the number of subjects aged 70 to 79 years was 6,837 and 6,856, and aged ≥ 80 years 1,921 and 1,917 in the HZ/su and placebo groups, respectively.

Results of the co-primary endpoints

VE against HZ in subjects ≥ 70 years of age (co-primary objective)

In the mTVC, after a median follow up of 4.0 years, there were 25 and 284 cases of HZ in the HZ/su and placebo groups, respectively. The incidence rate was 0.8 and 9.3 per 1000 person years, respectively. The VE for preventing HZ was 91.30% (95% CI: 86.88 to 94.46%, $p < 0.0001$). VEs were consistent in both the 70 to 79 and the ≥ 80 years of age groups (91% in both). In these subjects aged ≥ 70 years, at year 4 the HZ VE was 87.9% (95% CI: 73.3 to 95.3).

VE against PHN in subjects ≥ 70years of age (co-primary objective)

There were 40 cases of PHN with 4 in the HZ/su group and 36 in the placebo group. The incidence was 0.1 and 1.2 per 1000 person years, respectively. The VE for preventing PHN was 88.78 (95% CI: 68.70 to 97.10%, $p < 0.0001$). For the 70 to 79 years of age group the PHN VE was 93.0% (95% CI: 72.5 to 99.2). The VE was not demonstrated in the ≥ 80 years of age subjects (PHN VE of 71.2%, 95% CI: -51.5-97.1%), and this is likely due to small numbers (2 cases in the HZ/su and 7 in the placebo group).

Results of the secondary endpoints

VE against PHN in subjects ≥ 50 years of age

For the overall population (≥ 50 years of age), the PHN VE was 91.22% (95% CI: 75.95 to 97.70%, $p < 0.0001$). Results from pooled analyses of the TVC and the ATP cohort were in line with the mTVC.

VE against PHN in subjects ≥ 50 years of age with confirmed HZ

On request from CBER and CHMP;[11] VE against PHN was assessed in subjects ≥ 50 years of age with confirmed HZ, and was included as a secondary objective. However, under the

[11] CBER: Center for Biologics Evaluation and Research (FDA); CHMP: Committee for Medicinal Products for Human Use (EMA)

assumption that HZ/su would be efficacious against HZ, the demonstration of an incremental efficacy against PHN, in addition to the PHN efficacy that is the direct consequence of HZ prevention, would have required a prohibitively large sample size. Therefore, the analysis of PHN prevention in subjects with confirmed HZ was not adequately powered.

In those ≥ 50 years of age, 4/32 (12.5%) subjects with confirmed HZ in the HZ/su group and 46/477 (9.6%) subjects in the placebo group developed PHN. In those subjects with confirmed HZ cases, VE against PHN was 0.29% (95% CI: -161.53 to 65.57, p < 0.5417). There was no significant reduction in the incidence of PHN and so the VE in preventing PHN is likely due to its effect on HZ.

VE for preventing HZ related complications (other than PHN, secondary objectives)

In view of the unexpectedly high VE against HZ, the company decided to run an additional post-hoc analysis to evaluate the overall VE in preventing HZ associated complications (other than PHN).

The analysis was performed on the pooled data. When considering all adults ≥ 50 years of age, the VE was 93.71% (95% CI: 59.53 to 99.85), with 1 case in the HZ/su group versus 16 cases in the Placebo group. When considering all adults ≥ 70 years of age, VE was 91.62% (95% CI: 43.38 to 99.80), with 1 case in the HZ/su group versus 12 cases in the Placebo group.

VE in reduction in duration of severe worst pain in subjects ≥ 70 years of age

The VE in reducing the duration of severe 'worst' HZ associated pain was evaluated as a secondary objective in the two pivotal studies and the pooled analysis. Due to the high VE against HZ, the studies lacked statistical power to demonstrate efficacy against this endpoint. However, when considering the descriptive statistics of the median duration of severe worst HZ associated pain in number of days, there was a trend for a shorter duration in the HZ/su group versus Placebo group in all analyses, that is, 11.0 versus 15.0 days in ≥ 50 years of age in Study ZOSTER-006, 13.5 versus 19.0 days in ≥ 70 years of age in Study ZOSTER-022, and 11.5 versus 19.0 in ≥ 70 years of age in the pooled analysis.

Other relevant clinical studies

Study ZOSTER-007; Lot consistency study

Study ZOSTER-007 (Lot consistency study): Consistency in terms of anti-gE Ab response was demonstrated between three HZ/su lots formulated from commercial-scale gE and $AS01_B$.

Study ZOSTER-004; Concomitant administration with influenza vaccine

Study ZOSTER-004 (Concomitant administration with influenza vaccine): co-administration with quadrivalent seasonal influenza vaccine found no evidence of immunological interference.

Study ZOSTER-033; in subjects with previous HZ

Study ZOSTER-033 (in subjects with previous HZ): this Phase III study was designed to assess the immune response of HZ/su in adults ≥ 50 years of age with history of a previous HZ. The study was an uncontrolled, open label trial. A total of 96 adults received 2 doses of HZ/su 2 months apart. The vaccine response rate was 90.2% (95% CI: 81.7; 95.7). This is above the pre-specified criterion to meet the primary objective related to immunogenicity and is consistent with what has been observed in other clinical studies where HZ/su was given to adults of same age with no HZ history.

Studies ZOSTER-001 and ZOSTER-015; immunocompromised subjects

Studies ZOSTER-001 and ZOSTER-015 (immunocompromised subjects): the two Phase I/II studies were designed to assess the safety and immunogenicity of HZ/su in immunocompromised (IC) population ≥ 18 years of age, that is, autologous HCT recipients in Study ZOSTER-001 and HIV infected subjects in Study ZOSTER-015. In both studies, a total of 135 recipients (73 were ≥ 50 years of age) showed high CMI and humoral gE-specific and VZV specific vaccine induced immune responses and the immune responses persisted until 1 year post last vaccination. Further studies in a larger population are necessary before more definite conclusions can be drawn.

Safety

The total exposure to HZ/su in the studies included in the dossier was 17,204 subjects. The main safety pool, which contained data from the two pivotal Phase III studies, included 14,745 adults ≥ 50 years of age who received at least one dose of HZ/su vaccine. Of these, approximately 95% received two doses of vaccine. The median follow up period was 3 years.

The HZ/su vaccine was reactogenic with a high rate (overall rate per dose) of local symptoms of pain (68%), redness (38%) and swelling (26%) as well as of general symptoms of myalgia (33%), fatigue (32%) and headache (26%). Other common symptoms were GI disorders (nausea, vomiting, diarrhoea and/or abdominal pain) (10.7%), shivering (17.6%) and fever (12.8%).

Most reactions were Grade 1 or 2 and symptoms tended to last less than 4 days. Severe, Grade 3, local symptoms were reported in ≤ 6.4% of subjects (pain being the most frequent) and Grade 3 general symptoms in ≤ 5.3% (fatigue and myalgia the most frequent). It was noted that the rate of Grade 3 general symptoms increased with the second dose of HZ/su (5.7% to 8.0%).

The safety data indicate that local and general solicited symptoms rate tends to be higher in 50 to 69 years of age group than the ≥ 70 years of age subjects.

The rate of SAEs (fatal and non-fatal) was similar between groups in the main safety pool (12.8% versus 13.3%, RR = 0.97 (95% CI: 0.91-1.03) unadjusted p = 0.316) and there were no evident safety signals. Rates were similar between treatment groups in the two main age groups.

In the briefing document to the Vaccines and Related Products Advisory Committee of the FDA (13 September 2017 meeting) imbalances in a number of conditions were noted including optic ischaemic neuropathy, temporal arteritis, amyotrophic lateral sclerosis, osteonecrosis and convulsions. It was also noted in the EU regulatory evaluation that the sponsor has been asked to comment on whether the adjuvanted vaccine has shown any evidence of impact on the immune system that may increase the risk of infections or malignancy. Apart from the finding on ovarian cancer (0.05% versus 0%), there were no evident signals on SAE rates.

Fatal SAEs in the study was comparable between HZ/su and placebo groups (4.3% versus 4.6%) and rates were also similar in the two age groups (50 to 69 and ≥ 70 years of age). Only one death was deemed treatment related by an investigator (neutropaenic sepsis in a 90 year old subject with AML diagnosed 75 days post vaccination).

It is also noted that there was an increased risk of arthralgia in the 30 day post vaccination period (1.72% versus 1.17%, RR = 1.48, 95% CI: 1.21 to 1.80). There was also a higher risk of gout or gouty arthritis in the period (0.18% versus 0.05% RR = 3.38, 95% CI: 1.49 to 8.60) (see Attachment 2, Table 49). The sponsor stated that gout was an immune inflammatory event of interest.

Data on medically attended visits were stated to have been collected to Month 8; however pooled data on associated adverse events could not be located.[12] The sponsor has been asked to discuss these events. In the response to questions, the sponsor states that the analysis of unsolicited AEs with medically attended visit by age group did not show any notable between group differences.

During the whole follow up period the withdrawal rate due to non-serious AEs was 0.5% versus 0.2% and due to an SAE was 4.7% versus 4.9%. The rate of discontinuation of vaccination due to an AE was slightly high in the HZ/su group due to known vaccine related symptoms; however discontinuation of vaccination due to SAE was not high in HZ/su group.

There were no notable differences between the HZ/su and placebo groups in the rates of pIMDs in the main safety pool (1.2% versus 1.4%) and about half the events were reported over one year post vaccination. Such events are rare and despite the sample size of about 15,000 there may be insufficient data to adequately detect such a risk. The event of pIMD should be included in the PI as adverse events.[13] It is noted that the risk of a pIMDs following the vaccination is included as an important potential risk in the RMP. Routine and enhanced surveillance will follow up the risk in post-marketing phase and a targeted safety study is planned. The safety in elderly patients with pre-existing immune mediated disorders is included as missing information and will be followed up by post-marketing surveillance.

There was one report of 'anaphylaxis' which did not require treatment and no increased rate of hypersensitivity reactions. There were also no clinically relevant changes in laboratory parameters in the studies where these were assessed.

There are limited safety data for the use of the vaccine in individuals with prior history of HZ. The risk of VZV reactivation following vaccination will be assessed in post-marketing studies. The product development in the immunocompromised population is ongoing and to date in the limited population of autologous HCT recipients and HIV infected subjects no safety concerns were evident.

There are no data in pregnant or lactating women and data in adults under 50 years of age are limited. There are no data as yet on the need for or safety of a booster dose of vaccine.

HZ/su given with quadrivalent seasonal influenza vaccine increased local and general solicited symptom rates and it is recommended that this is noted in the PI.

Risk management plan

The second round RMP evaluation report was included for an ACV meeting. Of note, the evaluator recommends to the Delegate that the PI should include a precaution statement such as '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'. The evaluator stated in the second round evaluation that the sponsor does not agree to the inclusion of pIMD (potential Immune Mediated Disorders) as adverse events in the PI.

In the sponsor's response to the second round RMP evaluation which was submitted to the TGA on 27 April 2018 (included for the ACV meeting), the sponsor agreed to include the above information in the Shingrix PI.

The suggested wording for the condition of registration was provided.

[12] Clarification: Data on medically attended visits was only collected for individual studies, not pooled.
[13] Clarification: It was agreed during the evaluation that pIMD events did not need to be included in the adverse events section of the PI.

Risk-benefit analysis

Delegate's considerations

In the submitted pivotal studies, Shingrix demonstrated a high efficacy against herpes zoster of about 97% in adults 50 years and older and importantly a high efficacy of about 91% in those aged 70 years and older. The currently available zoster vaccine, Zostavax, has a lower reported efficacy particularly in those aged ≥ 70 years. While there are no head-to-head comparisons, the efficacy results in this dossier for Shingrix are compelling.

In terms of efficacy against PHN in subject's regardless if they had confirmed HZ or not, Shingrix demonstrated efficacy of 100% in those aged ≥ 50 years of age. From pre-specified pooled data analysis, the efficacy against PHN in those aged 70 years and older was demonstrated at approximately 88%.

For those with confirmed HZ, there was no significant reduction in the incidence of PHN (VE of 0.29%, 95% CI: -161.53% to 65.57%). The efficacy of Shingrix in the prevention of PHN in subjects with confirmed HZ could not be confirmed. The benefits of Shingrix in the prevention of PHN are attributed to the efficacy of the vaccine on the prevention of HZ, as the efficacy of Shingrix in prevention of PHN in subjects with confirmed HZ could not be confirmed.

The vaccine was noted to have high reactogenicity with local injection site reactions and general symptoms such fatigue, headache and myalgia. It is possible that in the clinical practice setting, this reactogenicity could interfere with second dose compliance. As the reactions subsided in a couple of days and are to some extent treatable, it is anticipated that this risk should be manageable. There were no major safety concerns although the database size of some 15,000 recipients limits its ability to detect very rare conditions. There was no increased rate of pIMD after a median safety follow up period of about 3 years. The vaccine has high immunogenicity and this might impact on the elderly population with pIMDs. The sponsor is planning further study to investigate the risk of pIMDs following vaccination and pIMD is included as a potential risk in the RMP.

Efficacy against HZ was demonstrated out to 4 years post vaccination however the issue of possible waning efficacy and the need for booster vaccination has not yet been defined. There are several areas where data are limited or lacking. These include:

- data on seronegative individuals (VZV naïve)
- data in individuals who have received Zostavax
- data on individuals with a history of herpes zoster
- data on the duration of protection beyond 4 years
- the need for booster vaccination
- data on immunocompromised population
- data on co-administration with vaccines other than influenza vaccine, such as pneumococcal vaccine and other adjuvanted vaccines.

Proposed action

Based on the above evaluation and discussion, the Delegate is of the view that the benefit-risk balance is favourable for the use of Shingrix in preventing herpes zoster in adults aged 50 years and older. The Delegate proposes to approve Shingrix for the revised indication below:

Shingrix is indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. The vaccine's effect on the prevention of post herpetic neuralgia (PHN) is attributed to the effect of the vaccine on the prevention of herpes zoster.

Request for ACV advice

The committee is requested to provide advice on the following specific issues:

1. Does the ACV consider that the benefits of Shingrix in the prevention of PHN are attributed to the efficacy of the vaccine on the prevention of HZ, as the efficacy of Shingrix in prevention of PHN in subjects with confirmed HZ could not be confirmed?
2. Does the ACV consider that the indication should be revised to:

   Shingrix is indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. The vaccine's effect on the prevention of post herpetic neuralgia (PHN) is attributed to the effect of the vaccine on the prevention of herpes zoster.
3. Does the ACV consider that the proposed dose interval of 'an initial dose followed by a second dose 2 to 6 months later' is acceptable?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Executive summary

The sponsor welcomes the TGA Delegate's positive recommendation to register Shingrix for persons ≥ 50 years.

Shingrix is a non-live Herpes Zoster adjuvanted recombinant subunit (HZ/su) candidate vaccine for the prevention of Herpes Zoster (HZ). This vaccine is designed to induce strong cellular and humoral immune responses in individuals with pre-existing immunity against Varicella Zoster Virus (VZV) and who are at increased risk of developing HZ.

The rate of HZ cases reported annually in Australia, in persons aged ≥ 50 years, is approximately 1000 cases per 100,000 population. HZ incidence rises with age.

Overall, an estimated 13% to 26% of patients with HZ develop complications. Complications occur more frequently with increasing age. Post herpetic neuralgia (PHN) is the most common complication of HZ. PHN is a neuropathic pain condition resulting from nerve damage caused by the reactivation of VZV in the ganglia that persists or occurs after the HZ rash itself has resolved.

Efficacy, immunogenicity and safety results from two pivotal studies, Study ZOSTER-006 (also referred to as Study ZOE-50) and Study ZOSTER-022 (also referred to as Study ZOE-70)) (adults ≥ 50 years of age (years of age) and adults ≥ 70 years of age, respectively), demonstrated Shingrix to be highly efficacious against HZ and its complications, such as PHN, in all age groups, with an acceptable safety profile.

The efficacy was also shown to persist for at least 4 years after vaccination.

There were no meaningful differences in efficacy against HZ and PHN across the different age groups, resulting in high vaccine efficacy (VE) in the oldest age group of subjects ≥ 70 years of age , who are most at risk for acquiring HZ and HZ related complications such as PHN.

The benefit-risk profile of Shingrix is thus favourable in adults ≥ 50 years of age.

GSK believe that the clinical data presented in this application show that Shingrix is a significant advancement on current therapeutic options for HZ and warrants registration.

TGA Delegate stated: 'While there are no head-to-head comparisons, the efficacy results in this dossier for Shingrix are compelling'.

Specific questions raised by the TGA Delegate for the ACV's advice

1. *Does the ACV consider that the benefits of Shingrix in the prevention of PHN are attributed to the efficacy of the vaccine on the prevention of HZ, as the efficacy of Shingrix in prevention of PHN in subjects with confirmed HZ could not be confirmed?*

The Shingrix Phase III clinical program, which measured VE on PHN, considered both the reduction of PHN incidence as a direct consequence of HZ prevention and the additional impact in reducing PHN in the subset of vaccinated individuals who may not be protected and may develop HZ; that is breakthrough cases of HZ.

Efficacy against HZ following vaccination with HZ/su was the primary objective of ZOSTER-006 (in subjects ≥ 50 years of age) and ZOSTER-022 (in subjects ≥ 70 years of age) and efficacy against PHN was a co-primary objective of the pre-defined pooling of these studies. HZ/su has been shown to be very efficacious in preventing HZ in adults 50 years of age and older (97.2% (95% CI: 93.7; 99.0)) and adults 70 years of age and older (91.3% (95% CI: 86.8; 94.5)). The incidence of PHN was also efficiently reduced as a direct consequence of HZ prevention. Indeed, HZ/su's efficacy in preventing PHN was 100.0% (95% CI: 77.1; 100.0) in adults ≥ 50 years of age and 88.8% (95% CI: 68.7; 97.1) in adults ≥ 70 years of age.

HZ VE was so high that there were not enough breakthrough HZ cases amongst vaccinated subjects (9 cases in adults ≥ 50 years of age (ZOSTER-006) and 25 cases in adults ≥ 70 years of age (ZOSTER-006 and ZOSTER-022 pooled) to show any statistically significant effect in further reducing the incidence of PHN. In subjects ≥ 50 years of age (ZOSTER-006): 0 cases of PHN out of 9 HZ cases in the HZ/su group versus 18 cases of PHN out of 254 HZ cases in the Placebo group were reported. In subjects ≥ 70 years of age (pooled ZOSTER-006 and ZOSTER-022), only 4 cases of PHN were reported out of 25 HZ cases in the HZ/su group versus 36 cases of PHN out of 284 HZ cases in the placebo group. It would have required a prohibitively large sample size (that is more than 300,000 subjects, or around 10 times larger than that of the conducted HZ/su efficacy studies) to be able to demonstrate a statistically significant effect.

However, several other pre-specified endpoints on HZ related pain were evaluated in the Phase III efficacy studies in subjects with at least one confirmed HZ episode following vaccination with HZ/su. For all HZ related pain endpoints (other than PHN), there was a consistent trend for a beneficial effect of HZ/su versus placebo and for several of these endpoints there was a statistically significant positive effect of HZ/su versus placebo on HZ related pain above and beyond the effect on HZ incidence, despite the very low number of breakthrough cases.

These data demonstrate the effect of HZ/su in reducing HZ related pain in subjects who develop breakthrough HZ. PHN is defined as the continuation (defined as beyond 90 days after rash onset) of HZ related pain observed at the time of and in the weeks following rash onset. Therefore, GSK is of the opinion there is no reason to conclude that HZ/su would not be able to efficiently prevent PHN in vaccinees who develop HZ even though this could not be statistically demonstrated due to the very high efficacy of HZ/su resulting in low number of breakthrough cases.

2. *Does the ACV consider that the indication should be revised to:*

> *Shingrix is indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. The vaccine's effect on the prevention of post herpetic neuralgia (PHN) is attributed to the effect of the vaccine on the prevention of herpes zoster.*

The sponsor respectfully does not agree that the Shingrix indication should be revised to that proposed by the Delegate above. The sponsor believes the indication agreed upon with the clinical evaluator should be retained:

> *Shingrix is indicated for the prevention of herpes zoster and post herpetic neuralgia in adults 50 years of age or older.*

This indication statement is simple, direct and factual in providing the clear message to prescribers and patients that Shingrix prevents both HZ and PHN. As highlighted by the clinical evaluator and the Delegate, Shingrix has been shown to be very efficacious in preventing both HZ (97.2% in adults ≥ 50 years of age and 91.3% in adults ≥ 70 years of age) and PHN (100.0% in adults ≥ 50 years of age and 88.8% in adults ≥ 70 years of age). In this contemplation, it is worth considering the indication for Zostavax; the only currently registered HZ vaccine as prescribers will be making a clinical choice based on the strength of the preventative measures in the indication:

> *Zostavax is indicated for the prevention of herpes zoster (shingles) in individuals 50 years of age and older. Zostavax is indicated for the prevention of postherpetic neuralgia (PHN) and for reduction of acute and chronic zoster-associated pain in individuals 60 years of age and older.*

Prevention of PHN, both overall and specifically in breakthrough HZ cases has been evaluated in clinical trials of Zostavax (in subjects ≥ 60 years of age) and HZ/su (in subjects ≥ 50 and ≥ 70 years of age). Although no head to-head comparative data are available, it is important to note that the methods for HZ and PHN case collection, as well as the algorithm for HZ case diagnosis and the PHN definition were identical in both vaccines' efficacy trials: PHN was defined as any HZ associated pain ≥ 3 (on a 0 to 10 scale) persisting or appearing more than 90 days after the HZ rash onset among evaluable cases.

Efficacy of Zostavax: The Shingles Prevention Study showed that vaccination with one dose of Zostavax in adults ≥ 60 years of age significantly reduced the incidence of HZ (VE = 51.3% (95% CI: 44.2; 57.6)) and overall PHN (VE = 66.5% (95% CI: 47.5; 79.2)) over a mean follow-up period of 3.1 years.[14] Although as noted by the Delegate, Zostavax has a lower reported efficacy in comparison to Shingrix, particularly in those aged ≥ 70 years of age.

Referring only to subjects who developed HZ after vaccination (breakthrough (BT) cases), a post-hoc analysis (Zostavax EPAR) suggests that vaccination slightly decreased the risk of subsequently developing PHN: in the Zostavax group, the risk of developing PHN after HZ was 8.6 %, versus 12.5 % in the placebo group, translating in a VE PHNBT of 38.5% (95% CI: 7.1%; 59.4%) in subjects ≥ 60 years of age.

Efficacy of Shingrix: As noted in response to Question 1, HZ VE was so high there were not enough breakthrough HZ cases amongst vaccinated subjects (9 cases in adults ≥ 50 years of age and 25 cases in adults ≥ 70 years of age) to show any statistically significant effect in further reducing the incidence of PHN. However, as discussed above, PHN VE, when considering all subjects regardless of whether they had confirmed case of HZ or not, was extremely high.

Effect of HZ vaccination on the HZ and PHN incidence from population perspective: These data indicate that vaccination with HZ/su has the potential to reduce the incidence of HZ and PHN to a lower level than vaccination with Zostavax. This conclusion is supported by data recently presented by the US Centers for Disease Control and Prevention (CDC) at the Advisory Committee on Immunisation Practices (ACIP) meeting.

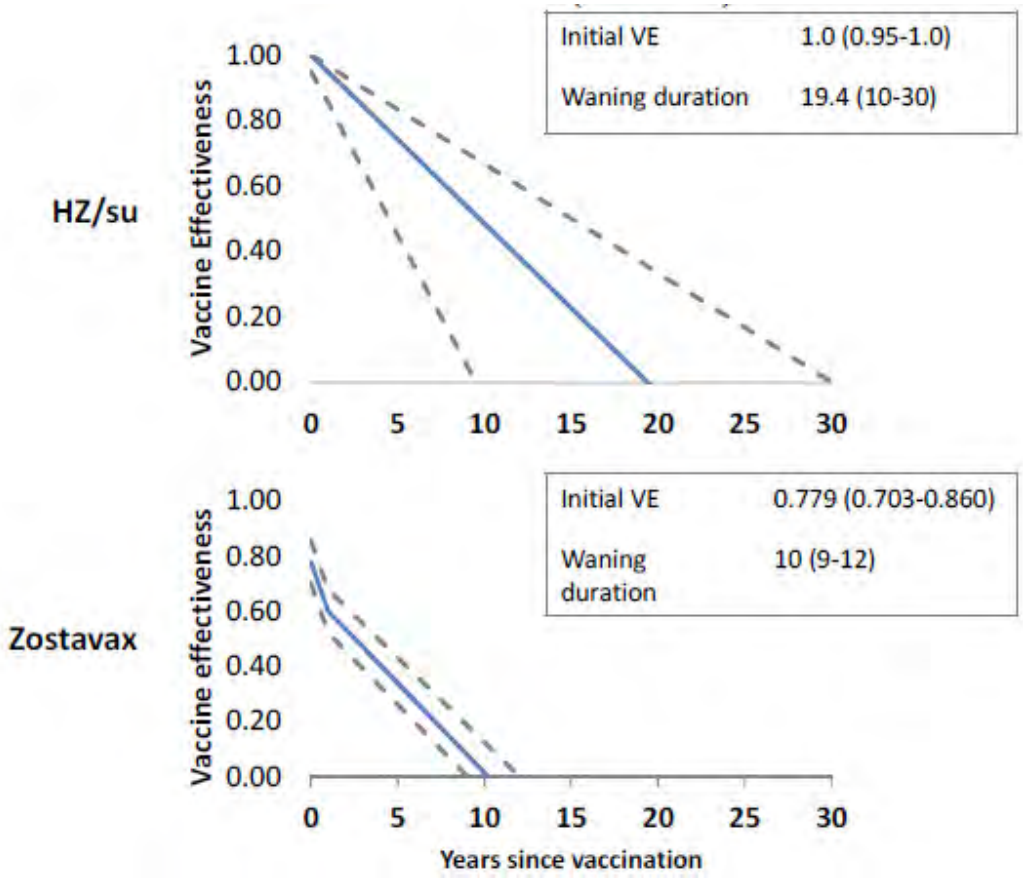
[14] Oxman MN, , et al. Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005; 352: 2271-2284

Table 9 presents projected HZ and PHN long-term efficacy data for HZ/su and Zostavax (without a booster dose). Note that the number of cases over an entire life time are being considered in a population of 1,000 persons and have been adjusted accounting for waning of vaccine efficacy, as presented in Figure 1. The sponsor considers this a conservative projection from the HZ/su's perspective as there is currently no evidence that HZ/su induced vaccine efficacy wanes over time.

Table 9: Projected number of cases of HZ and PHN over entire life time when vaccinated at specified age with HZ/su or Zostavax (US CDC)

	No vaccination	*Zostavax®*	HZ/su
Age at vaccination (YOA)	Number of Herpes Zoster cases		
50-59	265	231	186
60-69	204	170	117
70-79	138	119	61
80-89	81	77	23
90-99	42	42	7
Age at vaccination (YOA)	Number of PHN cases		
50-59 YOA	32	29	27
60-69 YOA	31	25	21
70-79 YOA	27	20	13
80-89 YOA	21	17	6
90-99 YOA	14	12	2

Figure 1: HZ vaccines' effectiveness in 60 to 69 years of age (US CDC)



These independent data confirm that vaccination with HZ/su has the potential to reduce the incidence of HZ and PHN to a lower level than vaccination with Zostavax, in all age groups.

Notably the CDC ACIP adopted the following recommendations:

- Shingrix is recommended for prevention of HZ and related complications for immunocompetent adults aged 50 years and older
- Shingrix is recommended for prevention of HZ and related complications for immunocompetent adults who previously received Zostavax
- Shingrix is preferred over Zostavax for prevention of HZ and related complications.

The TGA Delegate also highlighted 'The currently available zoster vaccine, Zostavax, has a lower reported efficacy particularly in those aged ≥ 70 years. While there are no head-to-head comparisons, the efficacy results in this dossier for Shingrix are compelling.'

In conclusion, the sponsor believes that the indication proposed by the Delegate may lead to ambiguity about HZ/su's ability to prevent PHN, and its possible public health impact and when compared, may unintentionally create the conclusion that Zostavax has additional features, not present in HZ/su, in preventing PHN. The sponsor proposes to retain the indication statement agreed with the clinical evaluator as it presents a clear message to prescribers and patients that HZ/su prevents both HZ and PHN.

3. *Does the ACV consider that the proposed dose interval of 'an initial dose followed by a second dose 2 to 6 months later' is acceptable?*

The sponsor supports retaining the flexibility of receiving the second dose of Shingrix between 2 and 6 months after the initial dose. Flexibility of the HZ/su dosing schedule is considered important from a public health perspective; a flexible administration timeframe for the second dose is expected to positively impact compliance with the second dose, which is important for inducing the most optimal protection against HZ, including long-term protection.

A 0 and2 month dosing schedule was used in the 2 pivotal Studies ZOSTER-006 and ZOSTER-022. Therefore, an addition Study ZOSTER-026, was conducted to evaluate vaccine response rate for anti-gE immune responses at one month post second dose in 0 and 6 month and 0 and 12 month schedule groups. Study ZOSTER-026 was an open label, randomised, parallel group immunogenicity study which assessed the two vaccination intervals in 354 adults ≥ 50 years. The 0 and 6 month schedule was found to be non-inferior to the 0 and 2 month schedule, however the 0 and 12 month vaccination interval did not meet the pre-defined non-inferiority criterion.

The Australian Technical Advisory Group on Immunisation (ATAGI) provided the below advice on the timing of the second dose in the ATAGI Pre-PBAC Submission Advice received by the sponsor in February 2018:

> *'Overall, ATAGI considers that the evidence of efficacy and safety has been adequately demonstrated for an interval between the 2 doses of 2 months and up to 6 months.'*

The full document has not been supplied at the request of ATAGI.

Other issues raised by the TGA Delegate

1. *There are several areas where data are limited or lacking. These include:*
   - data on seronegative (VZV naïve) individuals
   - data on individuals who have received Zostavax;
   - data on individuals with a history of herpes zoster
   - data on the duration of protection beyond 4 years and the need for booster vaccination;
   - data on immunocompromised population

The sponsor has addressed each of these points below:

Data on seronegative (VZV naïve) individuals: Studies ZOSTER-006 and ZOSTER-022 were not designed to assess the immunogenicity, safety and efficacy of HZ/su in seronegative patients, as a primary infection with either wild-type or vaccine-type VZV is a prerequisite for developing HZ.[15] Limited clinical data are available on the VZV immune status of subjects enrolled in the two pivotal clinical studies however less than 1% of subjects that were tested in the humoral immuno-subset were VZV seronegative at baseline.

Data on individuals who have received Zostavax: Study ZOSTER-048 was designed to evaluate the immunogenicity, safety, and reactogenicity of HZ/su in adults ≥ 65 years of age who were previously vaccinated with Zostavax. This study has now finished and will be submitted to the TGA as a post approval application when available. Please refer to the provided paper summarising the study results. The data does not indicate that safety signals are to be expected following HZ/su vaccination in previous Zostavax recipients, further noted the US CDC ACIP recommends vaccination with Shingrix for immunocompetent adults who previously received Zostavax.

Data on individuals with a history of herpes zoster: Study ZOSTER-033, submitted in the original application, assessed the reactogenicity, safety, and immunogenicity of Shingrix when administered to individuals with previous HZ. The efficacy and safety profiles of Shingrix in Study ZOSTER-033, was similar to that seen in other clinical studies in a population with no history of HZ. However, due to limitations with this study, GSK have committed to a new study, Study ZOSTER-062, to assess safety, reactogenicity, and immunogenicity of Shingrix in adults ≥ 50 years of age with a prior episode of Herpes Zoster. Further information on this study is included in the EU-RMP and Australian Specific Annex.

Data on the duration of protection beyond 4 years and the need for booster vaccination: The lack of data in this area and further information is addressed in the EU-RMP and Australian Specific Annex. Follow up studies in subjects who were previously vaccinated in a Phase II dose ranging study showed that while both humoral and cellular immune responses wane over time, at year 9 post first dose they were still above the pre-vaccination levels. Whether this translates into protection against HZ is unknown. Two studies (Studies ZOSTER-049 and ZOSTER-060) are planned to generate additional data on long term follow-up.

Data on immunocompromised population: The lack of data in this population, and further information is addressed in the EU-RMP and Australian Specific Annex. Studies ZOSTER-002, -028, -041, and -039 are ongoing and/or completed and will be subject to a future variation.

Data on co-administration with vaccines other than influenza vaccine, such as pneumococcal vaccine and other adjuvanted vaccines: As discussed in the response to questions, the end of study safety results from the Study ZOSTER-035 (HZ/su co-administration with Pneumovax 23) and end of study safety result of the Study ZOSTER-042 study (HZ/su co-administration with Boostrix) are now available. The available clinical data shows that there is no safety concern when HZ/su is co-administered with Boostrix or Pneumovax 23. Results from both studies will be submitted as post-approval variation. In addition, the sponsor is planning to conduct a co-administration study of HZ/su with Prevenar 13 (Study ZOSTER-059).

Conclusion

Shingrix has been shown to be highly efficacious against HZ and its complications, such as PHN, in all age groups, meaning a high VE in the oldest age stratum of subjects > 70 years of age who are most at risk for acquiring HZ and HZ related complications such as PHN.

[15] Cohen JI. Herpes zoster. *N Engl J Med*. 2013; 369: 255-263

Therefore, HZ/su is expected to provide a substantial clinical benefit, and help to address the medical need, especially in this age group. The efficacy was also shown to persist for at least 4 years after vaccination. Based on the results of the safety pooling data generated in approximately 15,000 HZ/su recipients > 50 years of age, no safety concern and no important risks have been identified. The sponsor would welcome the ACV aligning with the opinions of the TGA clinical evaluator and Delegate in recommending registration of Shingrix.

Advisory Committee Considerations

The Advisory Committee on Vaccines (ACV), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACV, taking into account the submitted evidence of efficacy, safety and quality, considered Shingrix vaccine , containing 50 µg recombinant varicella zoster virus glycoprotein E antigen ($AS01_B$ adjuvanted) as powder and suspension for injection, to have an overall positive benefit-risk profile for the revised indication sought by the sponsor:

> *Shingrix is indicated for the prevention of herpes zoster and post herpetic neuralgia in adults 50 years of age or older.*

In making this recommendation the ACV:

- noted the comprehensive clinical development program and on-going studies in immunocompromised patients, for whom data to date are limited
- noted that the efficacy data were favourable for both the prevention of herpes zoster (HZ), with vaccine efficacy of 97.2% (95% CI: 93.7; 99.0) in patients 50 years and older and 91.3% (95% CI: 86.8; 94.5) in patients 70 years and older, and for the prevention of post herpetic neuralgia (PHN), with vaccine efficacy of 100% in patients 50 years and older and 88.8% in adults 70 years and older
- noted the high rates of local (86.7%) and general (72.2%) symptoms following vaccination, including 24.4% of patients experiencing Grade 3 symptoms (vaccination-related reactions severe enough to prevent normal activities)
- noted the indication recently approved in the European Union
- noted the inclusion in the vaccine of an adjuvant not previously used in registered vaccines in Australia
- noted that the risk management plan appeared adequate although it could be enhanced with the use of Australian systems such as AusVaxSafety to accrue data more rapidly.

Proposed Product Information (PI) / Consumer Medicine Information (CMI) amendments

Given the number and range of on-going clinical trials in different population groups, including studies for which results are appearing in the public domain;[16] the ACV expected that the PI will be updated regularly in the early years of use. The ACV advised that, as soon as it becomes available for regulatory purposes, additional information should be

[16] For example, https://clinicaltrials.gov/ct2/show/results/NCT02045836?term=zoster+pneumovax&draw=3&rank=2&sect=X43ec0156&view=results

provided in the PI on co-administration with other vaccines, including if/where co-administration with another vaccine increases the rates of adverse reactions to Shingrix.

The PI should clearly describe the population groups where data are currently lacking, e.g., immunocompromised patients, patients with asplenia. For the small numbers of HIV positive recipients of the vaccine in trials, the two dose schedule appeared immunogenic (whether immunocompromised or not).

The ACV noted that Category B2 has been proposed as the Use in Pregnancy category; reflecting the limited data on the use of Shingrix in pregnant women. The CMI should be reviewed, as the advice to discuss the risks and benefits of vaccination during pregnancy or lactation is not relevant for the indicated female population of 50 years and older; as written, the CMI implies that the vaccine could be used in women of child-bearing age, which is not the case.

Specific advice

The ACV advised the following in response to the Delegate's specific questions on the submission.

1. *Does the ACV consider that the benefits of Shingrix in the prevention of PHN are attributed to the efficacy of the vaccine on the prevention of HZ, as the efficacy of Shingrix in prevention of PHN in subjects with confirmed HZ could not be confirmed?*

The ACV noted for adults over 50 years of age with HZ, 10 to 18% develop PHN as a complication. Similarly to HZ, the incidence of PHN increases with increasing age.

Due to the high vaccine efficacy for HZ, the power for analysis of secondary objectives of reduction in the incidence of PHN was estimated to be very small, due to the low number of confirmed HZ cases in the vaccinated groups in Studies ZOSTER-006 and ZOSTER-022. The ACV noted there were no convincing data to show that the vaccine affected the incidence of PHN in the subpopulation with breakthrough disease (that is where the vaccine failed to protect against HZ). However, the ACV advised that use of the vaccine would reduce the incidence of PHN in the indicated population. PHN is a condition that is difficult to treat and reduction in the risk of PHN is in itself a reason to administer the vaccine.

2. *Does the ACV consider that the indication should be revised to:*

> *Shingrix is indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. The vaccine's effect on the prevention of post herpetic neuralgia (PHN) is attributed to the effect of the vaccine on the prevention of herpes zoster.*

The ACV advised that overall the revised indication proposed by the sponsor, and recently approved in the European Union, was suitable for Australia.

3. *Does the ACV consider that the proposed dose interval of 'an initial dose followed by a second dose 2 to 6 months later' is acceptable?*

The ACV advised that the proposed interval of 2 to 6 months between the initial and second dose was acceptable. The committee noted that a dose interval of 2 months was used in both pivotal efficacy studies but that Study ZOSTER-026 had found that the 0 and6 month schedule was non-inferior to the 0 and 2 month schedule.

Other advice

The ACV noted that the clinical trial population in the pivotal studies showed a lower rate of HZ than expected, in comparison to the Australian population. The outcomes of the clinical studies, in a possibly healthier population, may have underestimated the favourable efficacy and safety outcomes for Shingrix.

The ACV noted that administration of paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) following vaccination was highly likely, whether suggested by a healthcare practitioner or self-selected, given the profile and severity of adverse events. However, there was no information in the PI, or in the clinical data, of the effect, if any, of co-administration of paracetamol or NSAIDs on antibody response and vaccine effectiveness. The ACV advised that Shingrix packaging should include the age group mentioned in the indication and the route of administration (intramuscular). Education for healthcare practitioners administering the vaccine should emphasise the high rate of adverse events, including Grade 3 reactions.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Shingrix recombinant Varicella Zoster Virus glycoprotein E antigen 50 micrograms powder and suspension for suspension for injection vial indicated for:

> *Shingrix is indicated for the prevention of herpes zoster and post herpetic neuralgia in adults 50 years of age or older.*

Specific conditions of registration applying to these goods

- Shingrix (recombinant varicella zoster virus (VZV) glycoprotein E (gE) vaccine) is to be included in the Black Triangle Scheme. The PI and CMI for Shingrix must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Shingrix EU-Risk Management Plan (RMP) (version 1.0, dated 25 January 2018, data lock point 12 October 2015), with Australian Specific Annex (version 2, dated April 2018), included with submission PM-2017-01784-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- Batch Release Testing and Compliance with the Certified Product Details
  - It is a condition of registration that all independent batches of Shingrix imported into Australia are not released for sale until samples and the manufacturer's release data have been assessed and you have received notification acknowledging release from the Laboratories Branch, TGA.
  - An electronic copy of the Certified Product Details (CPD) as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) should be provided upon registration of the therapeutic good.

Attachment 1. Product Information

The PI for Shingrix approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au