

7.04 VARICELLA ZOSTER VIRUS RECOMBINANT VACCINE, Injection [1 vial] & adjuvant substance diluent [0.5 mL vial], Shingrix[®], GlaxoSmithKline Australia Pty Ltd.

1 Purpose of resubmission

- 1.1 The standard re-entry submission requested a National Immunisation Program (NIP) listing for varicella zoster virus recombinant vaccine (RZV) for the prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN) for non-Indigenous people \geq 65 years of age (YOA) and Aboriginal and Torres Strait Islander people \geq 50 YOA.
- 1.2 Listing was requested on the basis of a cost-utility analysis versus no vaccine.

Table 1: Key components of the clinical issue addressed by the resubmission (as stated in the resubmission)

Component	Description
Population	<u>Population 1: Non-Indigenous adults 65 YOA, with a perpetual catch-up program for adults > 65 YOA.</u> ^a <u>Population 2: Indigenous adults 50 YOA, with a perpetual catch-up program for adults > 50 YOA.</u> ^a
Intervention	Recombinant Varicella Zoster Virus glycoprotein E antigen (AS01 _B adjuvanted) vaccine (RZV or Shingrix [®])
Comparator	Primary: RZV versus <u>no vaccine.</u> ^b Secondary economic comparison: Zoster vaccine live (ZVL or Zostavax [®]) versus no vaccine. Supplementary: RZV versus ZVL.
Outcomes	Efficacy: Cases of HZ, cases of PHN, and HZ-associated complications. Safety: Solicited local and general AEs, unsolicited AEs, and SAEs.
Clinical claim	RZV versus no vaccine: superior efficacy and 'slightly' inferior safety.

Source: Table 1-2, p23 of the resubmission

AE = adverse event; HZ = herpes zoster; PHN = post-herpetic neuralgia; RZV = recombinant zoster vaccine (Shingrix); SAE = serious adverse event; YOA = years of age; ZVL = zoster vaccine live (Zostavax).

^a The population in the 2018 submission was adults \geq 60 years for both Aboriginal and Torres Strait Islander and non-indigenous populations with a 5 year catch-up program for those >60 YOA.

^b The comparator in the 2018 submission was ZVL for adults aged 70-79

Underlined text highlights changes from previous submission

- 1.3 The resubmission did not clearly define a population of younger immunocompromised adults (\geq 18 YOA as currently TGA-indicated and as recommended in the 2022 ATAGI pre-submission advice) and no cost-effectiveness analysis is presented for this population. The resubmission stated 'the complexity of demonstrating cost-effectiveness in numerous at-risk cohorts would prove challenging for timely evaluation and PBAC approval'. As such, the resubmission indicated that 'a pragmatic decision could be made to extend access to younger at-risk populations, based on the assumption RZV cost-effectiveness demonstrated in the proposed NIP populations would also be applicable to immunocompromised adults at a younger age threshold, with similar or greater risk of HZ, and similar efficacy, immunogenicity, and safety of RZV'.

- 1.4 The immunocompromised populations for which a cost-effectiveness analysis was not presented in this resubmission are:
- Immunocompromised non-Indigenous adults 18 to 64 YOA; and
 - Immunocompromised Aboriginal and Torres Strait Islander adults 18 to 49 YOA.

2 Background

Registration status

- 2.1 RZV was TGA registered on 28 June 2018 for the prevention of HZ and PHN in adults 50 years and over. An extension of indication to include adults 18 years of age or older at increased risk of HZ was approved 13 December 2021.

Previous PBAC consideration

- 2.2 In November 2014 the PBAC recommended listing live zoster vaccine (ZVL) on the NIP for immunocompetent persons aged 70 years, with a catch-up cohort of persons aged 71 to 79 years. The catch-up for those aged 71 to 79 is in place until October 2023.
- 2.3 In November 2018 the PBAC did not recommend the listing of RZV on the NIP for the prevention of HZ in adults aged 60 years, with a five-year catch-up program. The PBAC considered that there was some uncertainty in the magnitude of the clinical benefit, the incremental cost-effectiveness ratios (ICERs) were highly uncertain and the estimated financial impact was high and uncertain. The PBAC considered more conservative cost-effectiveness analyses were required, given the large opportunity cost of listing (paragraph 7.1, RZV Public Summary Document [PSD], November 2018 PBAC meeting).
- 2.4 Updates in the resubmission included:
- Change in proposed population for NIP listing.
 - The proposed comparator is 'no vaccine' for all populations to reflect possible changes to supply of ZVL.
 - Presentation of additional clinical evidence which included:
 - longer-term follow-up data with interim data up to 10 years post-vaccination.
 - additional data for RZV in adults who have received prior ZVL, had a prior HZ infection, and for immunocompromised adults at increased risk of HZ.
 - clinical and post-marketing data on short-term RZV efficacy and effectiveness after one dose, as well as completion of the two-dose RZV schedule.
 - A price of \$11 per dose of RZV (5.4% lower than the 2018 submission).

For more detail on PBAC's view, see section 7 PBAC outcome.

Public Summary Document – March 2023 PBAC Meeting

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Population	Include evaluation of RZV for a lower age threshold of at least 50 years, as per ATAGI advice, for those who are (i) Aboriginal and Torres Strait Islander, or (ii) immunocompromised (Para 7.2, RZV PSD, November 2018).	Addressed for Aboriginal and Torres Strait Islander population (proposed NIP population, see Table 1). An economic analysis was not presented for non-Indigenous immunocompromised individuals aged 50-64.
Clinical effectiveness in certain subpopulations	The PBAC considered that the magnitude of benefit was uncertain as ZOE-50 and ZOE-70 excluded individuals who had previously received ZVL, previously had HZ; or who were immunocompromised or immunosuppressed (Para 7.5, RZV PSD, November 2018).	Supportive evidence was presented for these subpopulations.
Clinical effectiveness of single RZV dose and waning rate	The duration of protection after a single RZV dose is unknown (Para 7.5, RZV PSD, November 2018).	Clinical (up to 90 days) and post-marketing (up to 2 years) data are available to inform short-term RZV efficacy and effectiveness after one dose. However, longer-term effectiveness remains unclear.
Lack of longer-term data on waning effects and need for a booster	Limited data to assess waning of the RZV vaccine and the longer-term need for a booster (Para 7.6, RZV PSD, November 2018).	ZOSTER-049 provides an additional 4 years of follow up (8 years in total), with preliminary data up to 10 years. Uncertainty remains regarding the need for booster, particularly in light of the proposed younger age groups.
Economic analysis	The economic analysis did not consider those previously vaccinated with ZVL (Para 7.8, RZV PSD, November 2018).	Individuals previously vaccinated with ZVL were not included in the base case analyses. A scenario analysis was presented assessing the impact of prior ZVL vaccination for age cohorts: 70-79 and ≥ 80 YOA (Aboriginal and Torres Strait Islander and non-Indigenous populations separately).
Incidence rates of HZ and PHN	The PBAC considered a more conservative estimate than the BEACH data should be used (Para 7.9, RZV PSD, November 2018).	The base case model used the BEACH data (MacIntyre, 2015) with an updated source (Qian, 2021a) used in sensitivity analyses.
Waning rate of vaccine efficacy	The PBAC noted that the vaccine efficacy was assumed to decline slowly over time (with 50% loss of efficacy after approximately 19 years and a complete loss of efficacy after approximately 33 years). The PBAC considered that the duration of protection assumptions was uncertain and optimistic and a more conservative assumption would be appropriate (Para 7.10, RZV PSD, November 2018).	The previous PBAC submission relied on long-term extrapolation of RZV VE from the ZOE-50/-70 trials with a mean follow-up of 3.2 and 3.7 years, respectively. The resubmission used data from a long term follow up study with a mean follow-up of 7.1 years.

Public Summary Document – March 2023 PBAC Meeting

Component	Matter of concern	How the resubmission addresses it
Recommended base case	The PBAC considered that the economic model included in any future resubmission should enable comparison of vaccinating at different ages, re-vaccinating following vaccination with ZVL, and conservative assumptions around: - incidence of HZ and PHN without vaccination; - rate of waning used from Year 5; and - The proportion of individuals receiving both doses of RZV and the vaccine efficacy associated with receiving one dose only (Para 7.12, RZV PSD, November 2018).	The model has been amended to allow for comparison of different ages and re-vaccination following vaccination with ZVL. However, the inputs selected relating to incidence of HZ and PHN, waning rates and vaccine efficacy after receiving one dose only may not be conservative.

Source: Compiled during the evaluation from information sourced Table 1.1, p21-22 of the resubmission
BEACH = Bettering the Evaluation and Care of Health dataset; HZ = herpes zoster; NIP, National Immunisation Program; PHN = post-herpetic neuralgia; PSD = public summary document; RZV = varicella zoster virus recombinant vaccine; YOA = years of age; ZVL = live zoster vaccine

3 Requested listing

Name, Restriction, Manner of administration and form	Price requested by sponsor	Proprietary Name and Manufacturer
Recombinant Varicella Zoster Virus Glycoprotein E Antigen (AS01 _B Adjuvanted) Vaccine; powder and suspension for injection, 0.5 mL; Shingrix® GSK	\$ [REDACTED]	Shingrix® GSK

Category/Program:	NIP
Groups eligible for the requested NIP listing of Shingrix	Non-indigenous adults aged 65 years and over Aboriginal and Torres Strait Islander adults aged 50 years and over
Number and timing of doses	2 x doses of RZV administered 2-6 months apart. For subjects who are immunodeficient, immunosuppressed or likely to become immunosuppressed due to known disease or therapy, and who would benefit from a shorter vaccination schedule, the second dose can be given 1 to 2 months after the initial dose.

Source: Compiled during the evaluation from Table 1-8, p43 of the resubmission
NIP = National Immunisation Program; RZV = recombinant zoster vaccine

3.1 The ESC considered it would be informative to seek ATAGI advice on whether excluding vaccination with RZV for people who had received ZVL in the last 5 years or people who had been previously vaccinated with two doses of RZV (see paragraph 6.76) would be implementable.

For more detail on PBAC’s view, see section 7 PBAC outcome.

4 Population and disease

4.1 Herpes zoster or shingles is a localised, painful, vesicular skin rash resulting from the reactivation of latent varicella zoster virus (VZV). The rash is usually accompanied by acute pain which can be very severe and disabling. Pain from HZ can be divided into

three phases: 1) acute, lasting up to 30 days after rash onset; 2) subacute, lasting 30-90 days after rash onset, and 3) PHN, generally defined as lasting a minimum of 90 days after rash onset.

- 4.2 In Australia, greater than 90% of adults are at risk of HZ as they have previously been infected with VZV. The overall incidence of HZ in Australia was 5.6/1,000 persons-years (PYs) from 2006 through 2013, with incidence increasing with age: 6.3/1,000 PYs in adults 50-59 YOA, 13.7/1,000 PYs in adults 60-69 YOA, 15.3/1,000 PYs in adults 70-79 YOA, and up to 19.9/1,000 in adults ≥ 80 YOA (MacIntyre 2015). The ESC noted the incidence data reported here is based on BEACH data which may overestimate HZ incidence (see paragraph 6.40).
- 4.3 Immunocompromised individuals are at a significantly increased risk of developing HZ and associated complications, including those requiring hospitalisation. Incidence rates for the immunocompromised population vary according to condition or immunosuppressive therapy. The ATAGI pre-submission advice noted that conditions consistently found to have a substantially higher risk of HZ include haematopoietic stem cell transplant, solid organ transplant recipients, haematological malignancies and advanced or untreated HIV with CD4 counts $< 250/\mu\text{L}$ or those with a higher CD4 count unable to be established on effective anti-retroviral therapy. The ATAGI advice considered conditions with moderate risk include systemic lupus erythematosus and rheumatoid arthritis and conditions with a low risk included solid organ malignancies, inflammatory bowel disease, end-stage renal disease, asthma, diabetes, depression and chronic obstructive pulmonary disease. Additionally, the ATAGI advice stated that all individuals receiving regular high doses of systemic corticosteroids, disease modifying anti-rheumatic drugs (DMARDs) or chemotherapy are at high risk of HZ. The PBAC noted the ATAGI defined conditions at moderate risk as those with a higher risk of HZ and its complications than individuals ≥ 65 years of age.
- 4.4 PHN is the most common complication associated with HZ, and can greatly impact sleep, productivity, and quality of life (QoL). PHN occurs in 15% to 30% of individuals with HZ, with incidence increasing with age (MacIntyre 2015) and is commonly refractory to treatment.
- 4.5 ZVL (a live vaccine) is currently recommended and funded under the NIP for immunocompetent people aged 70 YOA (with catch-up for those aged 71-79 YOA in place until October 2023). RZV is proposed to replace ZVL in the current NIP clinical management algorithm with expanded coverage to non-Indigenous adults ≥ 65 YOA and Aboriginal and Torres Strait Islander adults ≥ 50 YOA (including both immunocompetent and immunocompromised people).
- 4.6 RZV is a non-live, adjuvanted recombinant zoster vaccine. The vaccine contains a recombinant VZV glycoprotein E (gE) with a novel adjuvant (AS01_B) designed to improve CD4+ T-cell mediated immune responses, which are important in preventing the reactivation of latent VZV. RZV is administered intramuscularly in 2 doses 2-6 months apart.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The resubmission nominated 'no vaccine' as the main comparator on the basis that ZVL may not be available on the Australian NIP from late 2023. The ESC noted some countries have discontinued the sale and supply of ZVL (USA in late 2020, New Zealand 2022) and local shortages have been reported¹.
- 5.2 The proposed comparator was updated from the 2018 submission, where the comparator was no vaccine for adults 60-69 YOA, ZVL for adults 70-79 YOA and no vaccine for adults ≥ 80 YOA. The resubmission included a supplementary comparison of RZV versus ZVL to reiterate the claim in the previous submission that RZV is superior to ZVL in terms of efficacy with a similar safety profile.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician noted the better efficacy and safety for RZV compared to ZVL. The clinician acknowledged the pivotal clinical studies for RZV (ZOE-50 and ZOE-70) excluded individuals who were immunocompromised and those who previously received ZVL or had HZ; however, noted the availability of additional data (including real world evidence) to support the use of RZV in these individuals. The clinician noted the high quality, long term data that is available for RZV relative to other vaccines in older individuals.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (9), health care professionals (16) and organisations (9) via the Consumer Comments facility on the PBS website. The comments from health care professionals and individuals note access to RZV will reduce HZ cases and associated morbidity in individuals, with the vaccine providing higher and longer efficacy compared to ZVL. The comments described the risks associated with ZVL (including death) for immunocompromised individuals, and noted RZV is the safer of the two vaccines. The input noted the significant impact of HZ and PHN on quality of life, including pain, inability to work, anxiety and depression and difficulty sleeping. The comments noted the significant equity issues associated with the high cost of RZV with wealthy individuals more likely to be able to afford the vaccine privately.
- 6.3 The PBAC noted the input received from Myeloma Australia and its Medical and

¹ <https://apps.tga.gov.au/shortages/Search/Tradename//130229>

Scientific Advisory Group regarding the importance of including RZV on the NIP for people who have multiple myeloma who are unable to receive ZVL. A number of organisations, including Immunisation Foundation of Australia (IFA) and Pain Australia, noted the significant impact of HZ infection on an individual's quality of life. IFA noted that RZV is a fairly reactive vaccine and consumers will need to be informed on the likelihood of a reaction, however it considered this would be manageable in clinical practice. The National Aboriginal Community Controlled Health Organisation (NACCHO) noted Aboriginal and Torres Strait Islander people are more likely to suffer from HZ and more likely to be immunocompromised so access to RZV is important. NACCHO noted RZV will be easier for nurses and Aboriginal health workers to administer as it will not require additional consideration of whether a live vaccine is appropriate as is required for ZVL. The Australian Rheumatology Association noted the reactivation of VZV is the most concerning infective complication in people treated with Janus Kinase (JAK) inhibitors and rheumatology patients are already at a higher risk of HZ due to their underlying conditions. Multiple Sclerosis Australia noted individuals with multiple sclerosis may be considered severely immunocompromised, and at significant risk of HZ, due to the immunosuppressant medications they may be receiving. The inclusion of RZV on the NIP was also supported by the Australian Society of Clinical Immunology and Allergy and the Pharmaceutical Society of Australia. A number of organisations were concerned with equity of access issues because of the high private cost of RZV.

Clinical trials

- 6.4 The resubmission was based on 2 head-to-head randomised efficacy trials comparing RZV and placebo (ZOE-50, ZOE-70) and a long-term follow-up study of these trials (ZOSTER-049).
- ZOE-50: Compared two doses of RZV to placebo in adults aged 50 years and over (N=15,411).
 - ZOE-70: Compared two doses of RZV to placebo in adults aged 70 years and over (N=13,900).
 - ZOSTER-049: Long-term follow-up study (ongoing) of ZOE-50 and ZOE-70 participants with interim analysis for vaccine efficacy against HZ (VE_{HZ}) (N=7,277).
- 6.5 The two pivotal trials (ZOE-50, ZOE-70) were considered by the PBAC in 2018.
- 6.6 The ZOSTER-049 study provides up to 10 years of follow-up of ZOE-50 and ZOE-70 participants. The resubmission included the second Year 4 interim analysis, performed after approximately 5 years follow-up of the ZOE 50/ZOE 70 participants and ≥ 4 additional years of follow-up in ZOSTER-49. Data from ZOSTER-049 has not previously been considered by the PBAC.
- 6.7 Details of the trials presented in the resubmission are provided in Table 3.

Public Summary Document – March 2023 PBAC Meeting

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
ZOE-50 (NCT01165177)	A phase III, randomised, observer blind, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01 _B vaccine when administered intramuscularly on a 0, 2-month schedule in adults 50 years and older. Lal, H., Cunningham, A., O., Godeaux, O. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults.	2015 <i>NEJM</i> 2015; 372, 2087-2096.
ZOE-70 (NCT01165229)	A phase III, randomised, observer blind, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01 _B vaccine when administered intramuscularly on a 0, 2-month schedule in adults 70 years and older. Cunningham, AL., Lal, H, Kovac M et al. Efficacy of the herpes zoster subunit vaccine in adults \geq 70 years of age	2016 <i>NEJM</i> 2016; 32: 1745-1753
ZOE-50 and ZOE-70 pooled	Curran, D., Oostvogels, L., Heineman, T et al. Quality of Life Impact of an adjuvanted Recombinant Zoster Vaccine in Adults aged 50 Years and Older. Kovac, M., Lal, H., Cunningham, A. L., Levin, M. J., Johnson, R. W., Campora, L., ... Heineman, T. C. Complications of herpes zoster in immunocompetent older adults: Incidence in vaccine and placebo groups in two large phase 3 trials. Curran, D., Kim, J. H., Matthews, S., Dessart, C., Levin, M. J., Oostvogels, L., ... Andrew, M. K. Recombinant Zoster Vaccine is Efficacious and Safe in Frail Individuals. Dagnew, A. F., Rausch, D., Hervé, C., Zahaf, T., Levin, M. J., & Schuind, A. Efficacy and serious adverse events profile of the adjuvanted recombinant zoster vaccine in adults with pre-existing potential immune mediated diseases: A pooled post hoc analysis on two parallel randomized trials. Oostvogels, L., Heineman, T. C., Johnston, R. W., Levin, M. J., McElhane, J. E., Van den Steen, P., ... Cunningham, A. L. Medical Conditions at enrolment do not impact efficacy and safety of the adjuvanted recombinant zoster vaccine: a pooled post-hoc analysis of two parallel randomized trials. Willer, D. O., Oostvogels, L., Cunningham, A. L., Gervais, P., Gorfinkel, I., Hyung Kim, J., ... Schuind, A. Efficacy of the adjuvanted recombinant zoster vaccine by sex, geographic region, and geographic ancestry/ethnicity: A post-hoc analysis of the ZOE-5- and ZOE-70 randomized trials.	2019. <i>The Journals of gerontology. Series A, Biological sciences and medical sciences</i> , 74(8) 1231-1238. 2018. <i>Vaccine</i> , 36(12) 1537-1541 2021. <i>Journal of the American Geriatrics Society</i> . 69(3), 744-752 2021. <i>Rheumatology (United Kingdom)</i> 60(3) 1226-1233. 2019. <i>Human vaccines and Immunotherapeutics</i> , 15(12), 2865-2872. 2019. <i>Vaccine</i> , 37(43), 6262-6267
ZOSTER-049 / ZOE-LTFU (NCT02723773)	Strezova, A., Diez-Domingo, J., Al Shawafi, K., Tinoco, J. C., Shi, M., Pirota, P., & Mwaking-Omari, A. (2022). Long-term Protection Against Herpes Zoster by the Adjuvanted Recombinant Zoster Vaccine: Interim Efficacy, Immunogenicity, and Safety Results up to 10 Years After Initial Vaccination.	2022. in <i>Open Forum Infectious Diseases</i> (Vol. 9, No. 20, p. ofac485).

Source: Adapted from Table 2.4, p63-66 of the resubmission.

6.8 A major difference between the ZOE-50 and ZOE-70 trials and the Australian setting is the ZOE trials excluded individuals with a history of HZ, those who had been previously vaccinated against HZ and those who were immunocompromised. The ATAGI noted that the use of strict eligibility criteria led to a healthier clinical trial population than in the general Australian population.

6.9 The key features of the direct randomised trials and long-term study are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
RZV vs. placebo (pivotal trials)						
ZOE-50	15,411	R, OB, MC, OL 3.2 years (mean, efficacy mTVC)	Low	Healthy individuals aged ≥ 50 years (mean 62.3 years)	Primary: Vaccine efficacy against HZ Secondary and exploratory: Vaccine efficacy against PHN, HZ complications, HZ mortality, HZ hospitalisations, HZ pain, immunogenicity and reactogenicity, ZBPI, EQ-5D, SF-36	Vaccine efficacy in terms of reduction in the incidence of HZ
ZOE-70	13,900	R, OB, MC, OL 3.7 years (mean, efficacy mTVC)	Low	Healthy individuals aged ≥ 70 years (mean 75.6 years)	As above	As above
RZV vs. placebo (long-term follow-up)						
ZOSTER-049	7,277	OL, MC, 9.6 years post vaccination (mean, efficacy mTVC)	Low	As above, combination of ZOE-50 and ZOE- 70 participants	Vaccine efficacy against HZ	Vaccine efficacy in terms of reduction in the incidence of HZ

Source: Collated during evaluation

HZ = herpes zoster; OB = observer blind; MC = multi-centre; mTVC = modified total vaccinated cohort; OL = open label; PHN = post herpetic neuralgia; R = randomised; RZV = recombinant zoster vaccine; ZBPI = zoster brief pain inventory.

Blue shading indicates information previously considered by the PBAC (2018 submission)

6.10 Vaccine efficacy against HZ and PHN were analysed on a modified total vaccinated cohort (mTVC) basis which excluded those who did not receive a second vaccine dose or who had confirmed HZ within 1 month after the second dose. The results therefore reflect the vaccine efficacy following 2 doses of RZV. The PBAC previously noted the proportion of individuals receiving two doses of RZV may be reduced in a population program compared with the clinical trial setting (paragraph 7.5, RZV PSD, November 2018 PBAC meeting).

6.11 Three additional trials (ZOSTER-033, ZOSTER-048, ZOSTER-046) and four observational studies (Izurieta 2021; Sun 2021a; Sun 2021b; Lu 2021) did not meet the screening inclusion criteria but were included as supportive evidence for those who have previously experienced HZ or previously received ZVL, as these populations were excluded from the ZOE-50 and ZOE-70 trials.

6.12 Six randomised, observer-blind placebo-controlled efficacy (predominantly immunogenicity) and safety studies on selected populations such as hematopoietic cell transplant recipients, HIV infected individuals, people with solid tumours receiving chemotherapy and those with renal transplant (ZOSTER-001, ZOSTER-002, ZOSTER-015, ZOSTER-028, ZOSTER-039, ZOSTER-041) were also presented in the resubmission as supportive evidence for immunocompromised populations.

Comparative effectiveness

Pivotal trials: ZOE-50 and ZOE-70

6.13 Table 5 presents a summary of the results of vaccine efficacy against HZ cases (VE_{HZ}) from the ZOE-50 and ZOE-70 trials.

Table 5: Results of vaccine efficacy against HZ cases (first or only episode) across the trials (mTVC)

Age strata	RZV				Placebo				VE_{HZ}^a			p-value
	N	n	T (year)	n/T (per 1000)	N	n	T (year)	n/T (per 1000)	%	Lower 95% CI	Upper 95% CI	
ZOE-50												
50-59 years	3492	3	11161.3	0.3	3525	87	11134.7	7.8	96.57	89.62	99.31	<0.0001
60-69 years	2141	2	7007.9	0.3	2166	75	6952.7	10.8	97.36	90.14	99.69	<0.0001
≥ 70 years	1711	1	5127.9	0.2	1724	48	5083.0	9.0	97.93	87.91	99.95	<0.0001
≥ 60 years*	3852	3	12135.7	0.2	3890	123	12035.7	10.2	97.58	92.77	99.51	<0.0001
≥ 50 years	7344	6	23297.0	0.3	7415	210	23170.5	9.1	97.16	93.72	98.97	<0.0001
ZOE-70												
70-79 years	5114	17	19346.5	0.9	5189	169	19247.5	8.8	90.02	83.54	94.32	<0.0001
≥ 80 years	1427	6	5058.5	1.2	1433	54	4920.3	11.0	89.08	74.65	96.16	<0.0001
≥ 70 years	6541	23	24405.1	0.9	6622	223	24167.8	9.2	89.79	84.29	93.66	<0.0001
Pooled ZOE-50 and ZOE-70												
70-79 years	6468	19	24410.9	0.8	6554	216	24262.8	8.9	91.27	86.04	94.85	<0.0001
≥ 80 years	1782	6	6314.6	1.0	1792	68	6151.9	11.1	91.37	80.22	96.94	<0.0001
≥ 70 years	8250	25	30725.5	0.8	8346	284	30414.7	9.3	91.30	86.88	94.46	<0.0001

Source: Table 2-14 and 2-15, p81-82 of the resubmission

mTVC = modified total vaccinated cohort; N = number of subjects included in each group; n = number of subjects having at least one HZ confirmed case; T (year) = sum of follow-up period (censored at the first occurrence of a HZ confirmed case) expressed in years; n/T (per 1000) = Incidence rate of subjects reporting at least one event; VE (%) = Vaccine Efficacy (Poisson method)

Notes: The modified vaccinated cohort excluded participants who did not receive the second dose of vaccine or who received a confirmed diagnosis of herpes zoster within 1 month after the second dose.

^a Vaccine efficacy in each age group was adjusted for region. Overall vaccine efficacy was adjusted for age group and region.

Blue shading indicates information previously considered by the PBAC (2018 submission)

* Statistical analysis of VE_{HZ} was planned for adults ≥50 years (primary objective, well powered), 50-59 & 60-69 years (secondary objective, appropriately powered), and ≥70 years (study not well powered under protocol assumptions although could lead to significance), but was not planned for adults ≥60 years. Therefore, presented results in this age group should be interpreted with caution.

6.14 Results of VE_{HZ} from the pivotal ZOE-50 and ZOE-70 trials showed that RZV resulted in a statistically significant reduction in HZ cases across all age groups. The VE_{HZ} was 97% (95% CI: 94%, 99%) in ZOE-50 and 90% (95% CI: 84%, 94%) in ZOE-70 and was reasonably similar across age groups. These results remain unchanged from those considered by the PBAC in the 2018 submission.

6.15 Results of vaccine efficacy against PHN (VE_{PHN}) from pooled results is presented in Table 6. VE_{PHN} appeared to be lower for the older age groups. The results were not statistically significant for the 60-69 YOA and ≥ 80 YOA groups, which may be due to

Public Summary Document – March 2023 PBAC Meeting

the small number of cases. These results remain unchanged from those considered by the PBAC in the 2018 submission. These results were not used in the economic model. The resubmission assumed $VE_{HZ} = VE_{PHN}$ in the economic model (this is discussed further in paragraph 6.52).

Table 6: Results of ZOE-50/70 pooled vaccine efficacy against PHN cases, overall (≥ 70 YOA) and by age group, (mTVC)

Age (years)	RZV				Placebo				VE_{PHN}^a			p-value
	N	n	T (year)	n/T (per 1000)	N	n	T (year)	n/T (per 1000)	%	Lower 95% CI	Upper 95% CI	
50-59 years ^a	3491	0	13789.7	0.0	3523	8	13928.7	0.6	100.00	40.88	100.00	0.0081
60-69 years ^a	2140	0	8621.4	0.0	2166	2	8674.4	0.2	100.00	-442.83	100.00	0.5097
≥ 50 years ^b	7340	0	28734.6	0.0	7413	18	28943.7	0.6	100.00	77.11	100.00	<0.0001
70-79 years ^a	6468	2	24438.8	0.1	6554	29	24660.4	1.2	93.04	72.47	99.19	<0.0001
≥ 80 years ^a	1782	2	6321.5	0.3	1792	7	6281.6	1.1	71.16	-51.51	97.08	0.1844
≥ 70 years ^b	8250	4	30760.3	0.1	8346	36	30942.0	1.2	88.78	68.70	97.10	<0.0001

Source: Table 2-16, p 82-83 of the submission.

LL = lower limit; mTVC = modified total vaccinated cohort; PHN, = post-herpetic neuralgia; RZV = recombinant zoster vaccine (Shingrix); VE = vaccine efficacy; UL = upper limit; YOA = years of age

N = number of subjects included in each group; n = number of subjects having at least one PHN case.

T (year) = sum of follow-up period (censored at the first occurrence of a PHN case) expressed in years

n/T (per 1000) = Incidence rate of subjects reporting at least one event.

Note: The modified vaccinated cohort excluded participants who did not receive the second dose of vaccine or who received a confirmed diagnosis of herpes zoster within 1 month after the second dose.

^a VE in each age group was adjusted for region.

^b VE adjusted by age strata and region.

Long-term follow-up study: ZOSTER-049

6.16 Table 7 presents the vaccine efficacy results against HZ from the (ongoing) long-term follow-up study, ZOSTER-049.

Public Summary Document – March 2023 PBAC Meeting

Table 7: Vaccine efficacy against HZ over time across the trials (mTVC) (second interim analysis)

Time	RZV				Placebo				VE _{HZ}			p-value
	N	n	T (year)	n/T (per 1000)	N	n	T (year)	n/T (per 1000)	(%)	Lower 95% CI	Upper 95% CI	
VE_{HZ} in ZOSTER-049 after 4 years of follow-up												
Overall ^a	7,277	52	32,673.8	1.64	7,277	283	32,673.8	8.7	81.6	75.9	89.8	<0.0001
VE_{HZ} from 1-month post-dose 2 in the ZOE-50/-70 trials												
	13,881	84	85,796.7	1.0	13,881	785	85,796.7	8.9	89.0	88.2	93.2	<0.0001
Year 1 ^b	13,881	3	13,744.5	0.2	14,045	130	13,823.3	9.4	97.7	93.1	99.5	<0.0001
Year 2 ^b	13,569	10	13,415.6	0.7	13,564	136	13,332.5	10.2	92.7	86.2	96.6	<0.0001
Year 3 ^b	13,185	9	13,016.1	0.7	13,074	116	12,834.0	9.0	92.4	85.0	96.6	<0.0001
Year 4 ^b	12,757	10	12,946.7	0.8	12,517	95	12,637.4	7.5	89.8	80.3	95.2	<0.0001
Gap between ZOE-50/-70 analysis and ZOSTER-049												
Year 6 ^a	7,277	7	7,210.2	1.0	7,277	61	7,210	8.5	88.5	74.9	95.6	<0.0001
Year 7 ^a	7,100	10	6,995.8	1.4	7,100	60	6,995.8	8.6	83.3	67.2	92.4	<0.0001
Year 8 ^a	6,878	9	6,762.9	1.3	6,878	57	6,762.9	8.4	84.2	67.9	93.1	<0.0001
Year 9 ^a	6,648	15	6,487.6	2.3	6,648	55	6,487.6	8.5	72.7	51.0	85.7	<0.0001
Year 10 ^{a,c}	6,258	11	4,896.1	2.3	6,258	41	4,869.1	8.4	73.2	46.9	87.6	<0.0001

Source: Table 2-17, p85 of the resubmission

HZ = herpes zoster; IR = incidence rate; LTFU = long-term follow-up; mTVC = modified total vaccinated cohort; N = number of individuals included in each group; n = number of individuals having at least one confirmed herpes zoster episode; PY = person-year; RZV = recombinant zoster vaccine (Shingrix); T (year) = sum of follow-up expressed in years; VE = vaccine efficacy.

Notes: The follow-up ceased at the first occurrence of a confirmed herpes zoster episode, last contact date, or data lock point for this second interim analysis. All efficacy estimates are adjusted by region.

^a RZV vs matched historical controls from the placebo group in the ZOE-50/70 studies.

^b RZV vs placebo recipients from the ZOE-50/70 trials adjusted for region.

^c At the data lock point data collection for year 10 was still incomplete.

6.17 Although VE_{HZ} remained high and reduction in HZ cases by RZV remained statistically significant, VE_{HZ} waned from 97.7% in Year 1 to 72.7% in Year 9. Data for Year 10 is incomplete, and the trial is estimated to be completed in January 2024. Data presented are for trial participants who have received both RZV doses. The ESC acknowledged the reduction in VE_{HZ} over time, with a marked reduction in Year 9 (but noted the wide CIs around the Year 9 estimate). The Pre-Sub-Committee Response (PSCR) stated the reported reduced VE in Year 9 coincides with the COVID-19 pandemic, which may have contributed to an increased risk of HZ in adults diagnosed with COVID-19 (Bhavsar, 2022). The PSCR stated subjects have also been lost to follow-up over time, due to the ageing population, contributing to increased variability of VE estimates in the long term follow up (LTFU) data. Furthermore, the PSCR noted estimates of RZV VE_{HZ} beyond Year 4 in ZOSTER-049 may be conservative, as adjustments for subject ageing and increasing risk of HZ over time were not included in the regression model for the historical control group. The ESC noted the referenced study (Bhavsar, 2022) did report a higher HZ risk in people ≥ 50 YOA diagnosed with COVID-19. However, the ESC considered this data may not be directly comparable to the Australian population due to the differing epidemiology of COVID-19 between countries. The ESC noted data reported by the NNDSS indicated a reduced number of

HZ cases reported for people ≥ 70 YOA between 2020 and 2022², which may reflect a reduced number of cases and/or reduced diagnosis/reporting.

Supportive evidence

- 6.18 The resubmission presented supportive evidence for the proposed NIP populations that were excluded from the ZOE-50 and ZOE-70 trials. This included immunocompromised people and individuals who previously experienced HZ or previously received ZVL.
- 6.19 Supportive evidence for individuals who have previously experienced HZ or previously received ZVL include:
- ZOSTER-033: An open label, single arm immunogenicity and safety study in people ≥ 50 YOA who previously have had HZ demonstrated its primary objective of a lower limit of the 95% CI $\geq 60\%$ anti-gE vaccine response rate (VRR) one month following a two-dose vaccination (81.7%). No safety concerns were identified in this study.
 - ZOSTER-048: An open label, group-matched multicentre immunogenicity and safety study comparing RZV in people ≥ 65 YOA who were previously vaccinated with ZVL ≥ 5 years prior compared to adults who never received ZVL showed that the immunogenicity profiles between the two groups were similar.
 - ZOSTER-046 (Weinberg, 2018): A randomized, double-blind, placebo-controlled immunogenicity trial stratified by age (50–59 and 70–85 YOA) demonstrated no difference in immunogenicity outcomes (cell-mediated immunity, CMI) for RZV between vaccine-naïve participants and prior ZVL recipients.
- 6.20 The resubmission also included four observational studies to support vaccine efficacy of RZV in adults who received prior ZVL (Izurieta 2021; Sun 2021a; Sun 2021b; Lu 2021). These were studies which compared VE_{HZ} in ZVL-naïve individuals and those with prior ZVL vaccination in the previous year (Lu 2021; Sun 2021a) or within 5 years (Sun 2021b; Izurieta 2021). VE_{HZ} among those > 65 YOA with prior ZVL vaccination within 5 years was 63% (95% CI, 58.3, 67.2) compared to 71.1% (95% CI: 69.5, 72.6%) in ZVL naïve people with an absolute difference of 8.1% (Izurieta 2021). ATAGI noted that this difference may have been driven by the lower rate of HZ incidence in individuals with ZVL vaccination compared to ZVL-naïve people and could be indicative of residual protection against HZ in those with prior ZVL.

² Analysis of NNDSS notifications of varicella zoster (shingles) cases for people aged 70 years and over available at <https://www.health.gov.au/resources/apps-and-tools/national-notifiable-diseases-surveillance-system-nndss-data-visualisation-tool>. Downloaded 29 Jan 2023

- 6.21 The ATAGI advice also noted that supportive studies showed favourable safety, robust immunogenicity and efficacy outcomes in those with history of HZ and those who previously received ZVL in the previous 5 years.
- 6.22 Supportive evidence on selected immunocompromised or high-risk populations such as hematopoietic cell transplant recipients, HIV infected individuals, people with solid tumours receiving chemotherapy and those with renal transplant were presented. These include:
- ZOSTER-001: A randomised, observer-blind, placebo-controlled immunogenicity and safety trial in those who had undergone autologous HSCT.
 - ZOSTER-002: A randomised, observer-blind, placebo-controlled efficacy and safety trial evaluating the VE_{HZ} of RZV in autologous HSCT recipients. The VE_{HZ} in adults was reported to be 68.2% (95%CI: 55.5, 77.6) ($p < 0.0001$) (median follow-up of 21 months).
 - ZOSTER-015: A randomised, observer-blind, placebo-controlled study evaluating safety and immunogenicity in HIV-infected adults at high risk of HZ.
 - ZOSTER-028: A randomised, observer-blind, placebo-controlled immunogenicity and safety trial in adults with solid tumours receiving chemotherapy.
 - ZOSTER-039: A randomised, observer-blind, placebo-controlled immunogenicity and safety trial in adults with haematologic malignancies. A post-hoc analysis reported a VE_{HZ} of 87.2% (95%CI: 44.3, 98.6) (median follow up 11.1 months).
 - ZOSTER-041: A randomised, observer-blind, placebo-controlled, immunogenicity and safety trial in adults with renal transplant.
 - ZOE-50/-70 (post-hoc analysis): VE_{HZ} of 90.5% (95% CI: 73.5, 97.5%) in ZOE-50/70 participants with at least one pre-existing potential immune-mediated disorders (pIMD), with the lowest being 84.4% (95% CI: 30.8, 98.3%) in the 70–79 YOA group.
- 6.23 The ATAGI pre-submission advice noted that for immunocompromised adults aged 18- 49 years, RZV is the only vaccine indicated and available to prevent HZ and ATAGI recommended that immunocompromised adults ≥ 18 YOA be considered as a separate NIP cohort. ATAGI noted that supportive studies showed favourable safety, robust immunogenicity and efficacy outcomes in adults ≥ 18 years at increased risk of HZ.

Comparative harms

- 6.24 Table 8 summarises the key adverse events in the ZOE trials.

Table 8: Summary of key adverse events in the randomised trials

Adverse Events	Type	RZV pooled ZOE-50/70		Placebo	
		N=14,645	%	N=14,660	%
Solicited local symptoms reported during the 7-day post-vaccination period					
Injection site pain	Any grade	3365	22.98	252	1.72
	Grade 3	212	1.40	5	0.0
Injective site erythema	Any grade	1357	9.27	37	0.25
	Grade 3	58	0.40	0	0.0
Injective site swelling	Any grade	1014	6.92	22	0.15
	Grade 3	42	0.30	0	0.0
Solicited general symptoms reported during the 7-day post-vaccination period					
Pain	Any grade	9973*	68.10	1012*	6.9
	Grade 3	557*	3.80	29*	0.2
Myalgia	Any grade	478	3.26	105	0.72
	Grade 3	63	0.40	8	0.1
Fatigue	Any grade	522	3.56	140	0.95
	Grade 3	62	0.40	7	0.0
Headache	Any grade	954	6.51	445	3.04
	Grade 3	99	0.70	27	0.2
Chills	Any grade	516	3.52	35	0.24
	Grade 3	87	0.60	2	0.0
Fever	Any grade	1037	7.08	76	0.52
	Grade 3	138	0.90	10	0.10
GI	Any grade	197	1.35	69	0.47
	Grade 3	26	0.20	6	0.0
Unsolicited AEs reported during the 30-day or 1-year post-vaccination period					
All AEs	30 days post-vaccination	7393	50.5	4689	32.0
Grade 3 AEs	30 days post-vaccination	1094	7.5	563	3.8
Related AEs	30 days post-vaccination	5052	34.5	968	6.6
SAEs	30 days post-vaccination	342	2.3	327	2.2
	1 year post vaccination	1482	10.1	1525	10.4
AEs with fatal outcomes	30 days post-vaccination	17	0.1	21	0.1
	1 year post vaccination	153	1.0	168	1.1
pIMD (AE of special interest)	30 days post-vaccination	30	0.2	30	0.2
	1 year post vaccination	90	0.6	105	0.7
	Related; 1 year post-vaccination	15	0.1	15	0.1

Source: López-Fauqued (2019), Table 1 to Table 4 and Table 2-23, 2-24 and 2-25, p93-94 of the resubmission

AE = adverse event; CI = confidence interval; GI = gastrointestinal; n = number of patients experiencing an AE; N = total number of patients; NR = not reported; pIMD = potential immune-mediated diseases; RZV = recombinant zoster vaccine; SAE = serious adverse event.

6.25 The safety of RZV was evaluated by pooling data from the ZOE-50 and ZOE-70 trials, involving 29,305 adults aged 50 years and older who received at least one dose of RZV (n=14,645) or placebo (n=14,660) administered according to the 0- and 2-month schedule. These results have been updated to reflect the pooled total vaccinated cohort across both trials.

6.26 The pooled safety analysis indicated the most frequently reported solicited local symptom following RZV was pain (68.1%). Reactogenicity was lower in the placebo group and pain was the most frequently reported solicited local symptom (6.9%). ATAGI noted ‘the incidence of solicited local and general symptoms was numerically lower in adults aged 70 years and older compared with those aged 50 to 69 years.

There was a higher incidence of pain and swelling at the injection site, fatigue, myalgia, headache, shivering, fever and gastrointestinal symptoms in adults aged 50 to 69 years compared with those aged 70 years and older. The overall frequency and severity of these events did not indicate a clinically meaningful different reactogenicity profile in the younger age strata'.

- 6.27 In the pooled safety analysis, 634 subjects (4.3%) in the RZV group and 680 subjects (4.6%) in the placebo group died during the entire study period. ATAGI had considered that none of the fatal cases were considered related to vaccination.
- 6.28 Long-term follow-up results from the ZOSTER-049 trial showed no deaths or other SAEs which were causally related to vaccination.

Benefits/harms

- 6.29 A summary of the comparative benefits and harms for RZV versus placebo (no vaccine) is presented in Table 9.

Public Summary Document – March 2023 PBAC Meeting

Table 9: Summary of comparative benefits and harms for RZV and no vaccine

Trial	N	VE, % (95% CI)	Event rate/year/1,000 individuals vaccinated ^a		Increment (per year per 1,000 vaccinated) ^b	
			RZV	PBO		
Benefits						
Reduction in HZ cases						
ZOE-50	14,749	97.16% (93.72, 98.97)	0.3	9.1	-8.8	
ZOE-70	13,163	89.79% (84.29, 93.66)	0.9	9.2	-8.3	
Pooled ZOE-50 and ZOE-70*	16,596	91.30% (86.88, 94.46)	0.8	9.3	-8.5	
ZOSTER-049 ^{c,d}	7,277	81.6% (75.9, 89.8)	1.6	8.7	-7.1	
Reduction in PHN cases						
ZOE-50	14,753	100% (77.11, 100.0)	0.0	0.6	-0.6	
ZOE-70	13,163	85.49% (58.52, 96.30)	0.2	1.1	-0.9	
Pooled ZOE-50 and ZOE-70*	16,596	88.78% (68.70, 97.10)	0.1	1.2	-1.1	
Harms						
	RZV n/N	PBO n/N	RR (95% CI)	Event /1,000 individuals vaccinated		RD ^b
				RZV	PBO	
Pain, Grade 3						
Pooled ZOE-50 and ZOE-70*	557/14,645	29/14,660	19.23 (NR)	38.03	1.98	36.06
Injection site erythema (any)						
Pooled ZOE-50 and ZOE-70	1,357/14,645	37/14,660	36.71 (26.50, 52.37)	92.66	2.52	90.14
Injection site swelling (any)						
Pooled ZOE-50 and ZOE-70	1,014/14,645	22/14,660	46.14 (30.30, 73.96)	69.24	1.50	67.74
Serious adverse events, at least one symptom						
Pooled ZOE-50 and ZOE-70	1,482/14,645	1,525/14,660	0.97 (0.91, 1.05)	101.19	104.02	-2.83

Source: Tables 2-14, 2-15 and 2-17 p81-85, and Tables 2-23 and 2-25 p93-95 of the resubmission and López-Fauqued (2019), Table 1 to Table 4

CI = confidence interval; HZ = herpes zoster; n = number of participants reporting data; N = total participants in group; NR = not reported; PBO = placebo; PHN = post-herpetic neuralgia; RD = risk difference; RR = relative risk; RZV = recombinant zoster vaccine SAE = serious

^a Mean duration of follow-up: ZOE-50 = 3.2 years; ZOE-70 = 3.7 years.

^b Calculated during the evaluation

^c Evidence not considered by the PBAC in the 2018 submission

^d Based on data collected after at least 4 years of follow-up in ZOE-LTFU and up to 10 years postvaccination in ZOE-50/70.

*Persons aged ≥70 YOA

6.30 On the basis of direct evidence presented by the resubmission, for every 1,000 individuals vaccinated with RZV in comparison to placebo (no vaccine) over a mean duration follow-up of 3.2 to 3.7 years:

- The number of cases of HZ would reduce by approximately 8 to 9 per year.
- The number of cases of PHN would reduce by approximately 1 per year

6.31 On the basis of direct evidence presented by the resubmission, for every 1,000 individuals vaccinated with RZV in comparison to placebo (no vaccine) over a median duration follow-up of 4.4 years:

- Approximately 36 additional individuals would experience Grade 3 pain.
- Approximately 90 additional individuals would experience any injection site erythema.

- Approximately 68 additional individuals would experience any injection site swelling.

6.32 The long-term follow-up results suggest a reduction in vaccine efficacy over time.

Clinical claim

6.33 The resubmission described RZV as superior in terms of effectiveness compared with placebo and slightly inferior in terms of safety compared to no vaccine (placebo) for the proposed NIP populations: non-Indigenous adults ≥ 65 YOA, and Aboriginal and Torres Strait Islander adults ≥ 50 YOA.

6.34 The ESC considered the claim of superior effectiveness was adequately supported for the proposed NIP populations; however, there was some uncertainty regarding the magnitude of benefit:

- The LTFU data shows a reduction in vaccine efficacy over time. This creates uncertainty around the long-term efficacy of the treatment, and the need for a booster in the future, which could impact the effectiveness and cost effectiveness of RZV.
- Immunocompromised people and individuals who have previously experienced HZ or have been previously vaccinated with ZVL were excluded from the pivotal trials. While supportive studies provided some evidence to demonstrate vaccine efficacy in these individuals, many were immunogenicity studies and there is currently no validated established immunological correlate of protection for HZ.

6.35 The ESC considered that while the supportive studies demonstrated RZV was likely to be effective and safe in immunocompromised people and individuals who have previously experienced HZ or have been previously vaccinated with ZVL, it remained uncertain if the vaccine effectiveness would be as observed in the ZOE studies.

6.36 The ESC noted the PBAC had previously considered the claim of inferior safety compared to no vaccine was reasonable (noting the increased frequency of injection site reactions compared to placebo) (paragraph 6.41, RZV PSD, November 2018 PBAC meeting). The ESC noted no new safety concerns relating to the vaccine have been identified.

6.37 The PBAC considered that the claim of superior comparative effectiveness was reasonable but agreed with the ESC that some uncertainty regarding the magnitude of benefit remained.

6.38 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.39 The type of economic evaluation presented was a cost-utility analysis. The model structure is the same as the 2018 submission. Major updates are summarised in Table 10.

Public Summary Document – March 2023 PBAC Meeting

Table 10: Summary of model structure, key inputs and rationale (for primary analysis)

Component	Resubmission	2018 submission
Population	Aboriginal and Torres Strait Islander adults ≥ 50 YOA Non-Indigenous adults ≥ 65 YOA	Adults ≥ 60 YOA
Comparison	RZV vs. no vaccine	60 and 80 years old: RZV vs. no vaccine 70 years old: RZV vs. ZVL
Time horizon	Maximum age of 100 years: up to 50 years for Aboriginal and Torres Strait Islander adults and up to 35 years for non-Indigenous adults in the model base case versus 10 years follow up in trial	Maximum age of 114 years: up to 54 years for adults in the model base case versus 3.2 to 3.7 years follow up in the trials
Outcomes	QALYs, direct healthcare costs, incremental cost per QALY (ICER), LYs, HZ cases, PHN cases, non-PHN HZ-related complications, HZ-related deaths	Unchanged
Methods used to generate results	Multi-cohort Markov model using cohort expected values	Unchanged
Health states	No HZ or complications HZ PHN Non-PHN HZ-related complication (ocular, neurological, disseminated, cutaneous) Recurrent HZ Death (absorbing)	Unchanged
Cycle length	1 year	Unchanged
Transition probabilities	Age-specific annual incidence of HZ and PHN – MacIntyre (2015) (BEACH 2006-2013) Age-specific risk of non-PHN HZ-related complications – Yawn (2007) Age-specific HZ-related mortality – Le and Rothberg (2015) Age-specific all-cause mortality – ABS (2021); ABS (2018b) Trial-based vaccine efficacy for HZ and PHN – ZOE-50 and ZOE-70 Vaccine efficacy waning for HZ and PHN – RZV: ZOSTER-049; ZVL (used for waning with only 1 dose of RZV): ZVL LTPS study	Unchanged Unchanged Unchanged Unchanged Unchanged Vaccine efficacy waning was only from ZOE-50 and ZOE-70
Extrapolation of VE over time	To estimate RZV take for VE_{HZ} (i.e. vaccine effectiveness immediately after vaccination), a linear regression was fitted to the annual VE_{HZ} estimates from year 1 to year 8 separately for adults 50-69 YOA and adults ≥ 70 YOA (Curran, 2021; Boutry, 2021). The intercept for each of these linear models was then used as the two-dose RZV take immediately after receipt of the second dose, while the respective slopes informed VE waning.	RZV VE were from ZOE-50 and ZOE-70 with a mean follow-up of 3.2 and 3.7 years, respectively Waning assumed to be 1.0% for the first four years following vaccination, 2.3% after four years before the age of 70, and 3.6% after turning 70.
Vaccine effectiveness against PHN	Assumes that $VE_{PHN}=VE_{HZ}$ for RZV	Unchanged

Component	Resubmission	2018 submission
Health related quality of life	McCaffery (2016) was identified as a study reporting equally applicable, but more recent, estimates during the preparation of this resubmission; this study is hence employed in the current model.	Utility values were informed by Clemens (2014) – an Australian EQ-5D-3L data set based upon Queensland population.

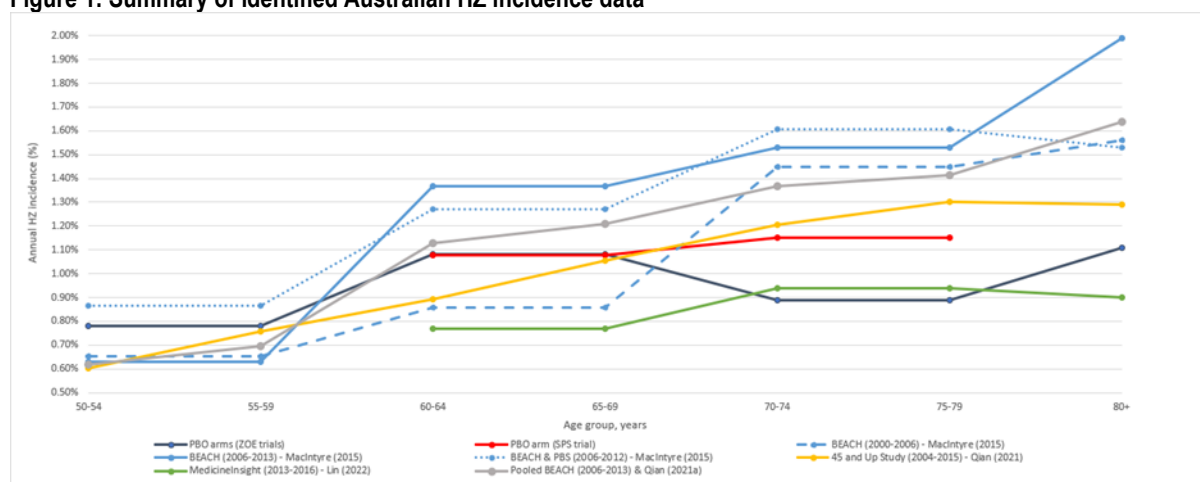
Source: Table 3.2, p110 of the resubmission.

ABS = Australian Bureau of Statistics; ATAGI = Australian Technical Advisory Group on Immunisation; BEACH = Bettering the Evaluation and Care of Health dataset; HZ = herpes zoster; ICER = incremental cost-effectiveness ratio; LTPS = long-term persistence study; LY = life-years; PHN = post-herpetic neuralgia; PBAC = Pharmaceuticals Benefits Advisory Committee; QALY = quality adjusted life years; RZV = Recombinant Zoster Vaccine; VE_{HZ} = Vaccine efficacy for HZ; VE_{PHN} = Vaccine efficacy for PHN; ZVL = Zostavax®

Incidence of HZ and PHN

6.40 The use of data from MacIntyre (as per 2018 submission) as the base-case may overestimate the incidence of HZ and PHN, thus favouring RZV. ATAGI pre-submission advice noted Qian (2021) and Lin (2022) are recently published Australian studies providing HZ incidence estimates in older Australians (≥ 45 YOA) and advised a pooled estimate from MacIntyre (2015), Qian (2021) and Lin (2022) could be used. Estimates from MacIntyre were higher than those presented in Qian 2021 and Lin 2022. For example, HZ incidence for ≥ 80 YOA, MacIntyre: 19.89 per 1000 persons; Qian: 13.31 per 1000 persons; and Lin: 9.3 per 1000 persons. See Figure 1 for more information (MacIntyre solid blue line, Qian yellow line, Lin green line).

Figure 1: Summary of identified Australian HZ incidence data



Source: Figure 3-3, p143 of the submission

6.41 The resubmission presented sensitivity analyses based on a pooled estimate from MacIntyre and Qian and using Qian alone. The ICER increased to \$25,000 to < \$35,000/QALY using pooled data from MacIntyre and Qian and to \$25,000 to < \$35,000/QALY using Qian alone. A sensitivity analysis conducted during the evaluation using data from Lin alone found the ICER increased to \$55,000 to < \$75,000/ QALY for the non-Indigenous population; and to \$115,000 to < \$135,000/ QALY for the Aboriginal and Torres Strait Islander population. An analysis using the pooled estimates from MacIntyre, Qian and Lin was not presented in the resubmission and the pooled data was not provided to enable a

sensitivity analysis during evaluation. The PSCR reiterated the discussion in the resubmission that Lin (2022) was not included in any pooled estimates as it was not designed to estimate the risk of HZ in the Australian population, as its case ascertainment method relies on free-text search and consistent GP encounter recording practices.

- 6.42 The ESC advised additional ATAGI guidance around the most reliable estimate of incidence would be informative. The ATAGI post-submission advice reiterated that the MacIntyre study may overestimate the HZ incidence and suggested that data from the MacIntyre (2015), Qian (2021) and Lin (2022) studies be combined to create one pooled point-estimate for the pre-vaccine HZ incidence. The pre-PBAC response reiterated that it was not appropriate to include the Lin study in the pooled estimate due to methodological issues. The pre-PBAC response acknowledged the incidence remains an area of uncertainty and stated the PBAC may wish to consider the cost-effectiveness of RZV using the base-case estimates from MacIntyre (2015) or using pooled incidence from MacIntyre (2015) & Qian (2021).
- 6.43 The resubmission used data derived from MacIntyre (2015) to estimate the age-specific incidence of PHN following a case of HZ. This is unchanged from the 2018 submission. ATAGI noted there is limited data and that MacIntyre (2015) was the most recent Australian data.
- 6.44 There are limited data regarding HZ incidence in Aboriginal and Torres Strait Islander people. The ESC noted incidence rate ratios for rates of hospitalisation for HZ from Sheel 2017 were used to inform adjustments to the baseline risk of HZ in Aboriginal and Torres Strait Islander population relative to the non-Indigenous population. The ESC considered the incidence in the Aboriginal and Torres Strait Islander population as uncertain but, overall, the approach in the resubmission was likely to be appropriate.

Vaccine efficacy

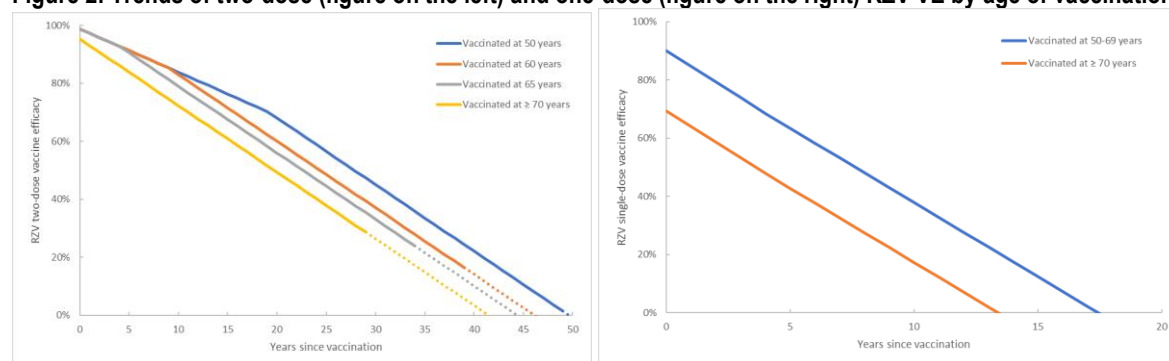
- 6.45 The resubmission applied a linear regression to fit the annual VE_{HZ} estimates from year 1 to year 8 separately for adults 50-69 YOA and adults ≥ 70 YOA from the first interim analysis of ZOSTER-049 (Curran, 2021; Boutry, 2021). The intercept for each of these linear models was then used as the two-dose RZV take after receipt of the second dose, while the respective slopes informed VE waning.
- 6.46 The estimated RZV two-dose VE_{HZ} take was 98.9% (95% CI: 94.0, 100.0) for adults 50-69 YOA and 95.4% (95% CI: 89.7, 100.0) for adults ≥ 70 YOA. These estimates have changed slightly from the 2018 submission – 98.4% and 97.8%, respectively, due to the inclusion of long-term follow-up VE data from ZOSTER-049.
- 6.47 Based on the linear regression models, the assumed annual waning rates were 1.5% for adults before the age of 70 years and 2.3% for adults older than 70 years (with no change in waning rates dependent on time after vaccination). With the exception of the rate used for the first 4 years following vaccination, the waning rates used in the

resubmission were lower than those used in the 2018 submission (1.0% for the first four years following vaccination, 2.3% after four years before the age of 70, and 3.6% after turning 70, refer to Table 13, RZV PSD, November 2018 PBAC meeting). Scenarios assuming an annual RZV waning rate of 5.4% beginning at 10 and 15 years were tested during the evaluation, demonstrating modest impact on cost-effectiveness results (refer to Table 15 and Table 16).

- 6.48 Single dose RZV VE_{HZ} was assumed to be 90.1% (for 50-69 YOA) and 69.5% (for ≥ 70 YOA) and given the absence of data and lack of long-term follow up for a single dose of RZV, the resubmission assumed the waning rate following a single dose to be the same as for ZVL (5.4% in years 1 to 4 and 5.1% from year 5 onwards). The ESC noted single dose VE_{HZ} was from a post-hoc analysis of all individuals in the ZOE-50 and ZOE-70 trials that received at least one dose of RZV. The ESC noted follow-up was short (76 days for ZOE-50 and 85 days for ZOE-70) and considered the VE_{HZ} of a single dose, and its rate of waning, remained uncertain.
- 6.49 Based on the rates used, the estimated duration of any protection for 1 dose was 17 years for those 50-69 YOA and 13 years for ≥ 70 YOA, compared to an estimated duration of protection for 2 doses of 50 years for those entering the model at 50 YOA. RZV remained partially effective in individuals over 50 YOA at the end of the modelled time horizon.

6.50 Figure 2 shows the RZV one- and two-dose VE waning across different age groups.

Figure 2: Trends of two-dose (figure on the left) and one-dose (figure on the right) RZV VE by age of vaccination



Source: Figure 3-7 and 3-8, p163, 164 of the resubmission.

RZV = recombinant zoster vaccine (Shingrix).

Notes: Dotted lines represent estimated VE beyond the age of 100 years (i.e., beyond modelled time horizon).

- 6.51 Although longer-term follow-up data was presented demonstrating vaccine efficacy up to 8 years (ZOSTER-049), there remains uncertainty around the long-term effectiveness of RZV given that the time horizon of the model is up to a maximum age of 100 years.
- 6.52 The resubmission assumed that vaccine efficacy against post-herpetic neuralgia (VE_{PHN}) was the same as VE_{HZ} . Given the very high efficacy of RZV in reducing HZ cases in the ZOE trials, there were few PHN cases to calculate VE_{PHN} in some age sub-groups. RZV VE_{PHN} in adults aged >70 YOA was 88.78% (95% CI: 68.70 to 97.10) (pooled ZOE-

50/70). The model applied a VE_{PHN} of 95.4% which the evaluation considered was not justified and not appropriate. The PSCR noted that ATAGI stated “no additional top-up efficacy for RZV can be calculated based on the limited number of breakthrough cases in the key trials, and therefore the assumption for RZV that VE_{HZ} is equal to VE_{PHN} appears reasonable” (ATAGI 2022 pre-submission advice, response to Q15, p108). The ESC agreed with ATAGI that this assumption was reasonable and further noted the vaccine efficacy for PHN did not have a significant impact on the ICER.

- 6.53 The ESC noted that Izurieta 2021 was a large observational study among individuals ≥ 65 YOA in the USA. Based on data from 15,589,546 unvaccinated people, 1,498,275 people vaccinated with 1 dose of RZV and 1,006,446 people vaccinated with 2 doses of RZV, the reported vaccine effectiveness against HZ (VE_{HZ}) of one dose was 56.9% (95% CI: 55.0, 58.8) and two doses was 70.1% (95%CI: 68.6, 71.5%). Sensitivity analysis using the two dose VE_{HZ} from this data found that ICERs increased to \$35,000 to $< \$45,000$ / QALY for non-Indigenous adults >65 YOA; and to \$95,000 to $< \$115,000$ / QALY for Aboriginal and Torres Strait Islander adults > 50 YOA. The ESC considered it would be informative to seek ATAGI advice on the clinical relevance of this study and whether it is appropriate to include it in the economic model. The ATAGI post-submission advice stated ZOE-50 and ZOE-70 were the appropriate data sources for the base case and the two dose vaccine effectiveness data from Izurieta 2021 could be used for sensitivity analysis.

Coverage

- 6.54 The resubmission assumed a two-dose vaccine compliance of 75% for adults 50-59 YOA (based on a 12-month series completion reported in Canada, McGirr, 2021) and 81% for adults ≥ 60 YOA (based on the midpoint of a 12-month series completion across post-marketing studies in Canada and the US). These estimates are higher than the 65% to 78% adherence recommended by ATAGI. Sensitivity analyses using 65% for 2-dose completion was conducted during the evaluation and resulted in minimal change in the ICERs. The ESC considered the impact of a lower second dose coverage was likely minimal as reduced second dose coverage reduces both effectiveness and vaccine cost.

Utilities

- 6.55 The estimated QALY loss per HZ or PHN case were based on the same values used in the 2018 submission (Gater, 2014; Serpell, 2014; Curran, 2017). Updated literature from Curran (2018a) and Curran (2019a) indicate that the QALY loss per HZ and PHN case incorporated into the economic model appears to be higher than those applied in published models and observed in ZOE trial participants. For example, Curran (2018a) applied a QALY loss for HZ without PHN of 0.005, 0.010 and 0.012 for age groups 50-59, 60-69 and 70+ YOA respectively, compared with a value of 0.023-0.024 in the current model. Further, Curran (2019a) also showed that utility loss (disutility) from a HZ event in ZOE-50 and ZOE-70 placebo arm participants decreased substantially from Day 0 to Week 4 in all age groups. For example, estimated utility

loss was 0.258 at Day 0 of an HZ episode and decreased to 0.008 by Week 4 compared to a constant disutility of 0.173 over approximately 7 weeks that was used in the model. The evaluation considered this remains a source of uncertainty and is highly influential on the cost-effectiveness of RZV.

- 6.56 The ESC acknowledged the utilities remain unchanged from the November 2018 submission. However, the ESC considered the QALY loss per case of HZ and PHN were overestimated. The ESC noted the ZOE-50 and ZOE-70 trial data demonstrated the expected attenuation of disease impact over the period of HZ. For example, trial data estimated a disutility of 0.258 at Day 0 of an HZ episode which decreased to 0.008 by Week 4 (assuming linear decline from week 0 to 4 the approximate QALY loss per HZ case would be 0.0175 i.e. $(0.258/2)*1$ (month)/12 (life year)). This is different to the economic model which applied a constant disutility of 0.173 over approximately 7 weeks (QALY loss of 0.02328 per HZ case i.e. $0.173*1.61$ (months) /12 (life year)). The ESC noted the ICER was sensitive to the assumed QALY loss per case. As ZOE-50 and ZOE-70 were the key source of clinical data in the resubmission, the ESC considered the utility values from these studies should have been used in the economic model.
- 6.57 The pre-PBAC response noted the example above was based on the utility loss in individuals aged 50 to 59 YOA and utility loss in individuals aged 60 to 69 YOA and ≥ 70 YOA remained high (0.008 and 0.035, respectively). The pre-PBAC response stated the assumption that all HZ cases resolve within 28 days is an underestimate for the populations most relevant for NIP listing. The pre-PBAC stated the base-case QALY loss estimates per HZ case were also conservative, as they did not incorporate differential QALY losses for breakthrough HZ cases in RZV-vaccinated subjects relative to unvaccinated subjects.

Resource use

- 6.58 Resource utilisation estimates were derived from a combination of sources which included MacIntyre (2019), Karki (2016) and Yawn (2007). The evaluation considered the hospitalisations per case of HZ with either PHN or non-PHN complications were high, ranging from 0.151 for those aged 50-59 years to 0.371 for those aged ≥ 80 years. The ESC noted a reduction in costs associated with HZ cases, PHN cases and non-PHN complications accounted for a high proportion of the cost offsets in the economic model (Table 12).

Model results

- 6.59 The key drivers of the model results are provided in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Age-specific annual incidence of HZ and PHN	Incidence is based on data from the BEACH 2006-2013 (MacIntyre, 2015)	High, favours RZV.
Vaccine efficacy	Data from ZOE-50 and ZOE-70. Efficacy at Year 0 was based on the intercept after fitting a linear function to trial data. It was assumed that $VE_{PHN} = VE_{HZ}$.	High, favours RZV. Alternate use of real-world effectiveness data (Izureita 2021) had a significant impact on the cost-effectiveness of RZV (up to a 113% increase in ICER)
QALY loss per HZ case with and without PHN	Data from Gater (2014), Serpell (2014) and Curran (2017).	High, likely favouring RZV.
Annual waning of vaccine efficacy	Data from ZOE-50, ZOE-70 and ZOSTER-049. Waning estimated by fitting a linear function to trial data.	Moderate, direction unknown
Discount rate	Base case 5%	Moderate, reducing the discount rate decreases the ICER.

Source: Compiled during the evaluation

BEACH = Bettering the Evaluation and Care of Health dataset; HZ = herpes zoster; PHN = post-herpetic neuralgia; VE_{HZ} , Vaccine efficacy for HZ; VE_{PHN} , Vaccine efficacy for PHN

6.60 The results of the economic evaluation for RZV vs. no vaccine are summarised in Table 12 and Table 13 for non-Indigenous adults >65 YOA and for Aboriginal and Torres Strait Islander adults >50 YOA, respectively.

Public Summary Document – March 2023 PBAC Meeting

Table 12: Results of the economic evaluation for RZV vs no vaccine – non-Indigenous adults ≥ 65 YOA

Result	RZV	No vaccine	Incremental difference	% of total difference
Case counts per million vaccinated				
HZ cases	105,944	280,510	-174,566	-
PHN cases	26,054	66,269	-40,214	-
Non-PHN complications cases	17,629	44,648	-27,018	-
Ocular	6,639	16,431	-9,792	-
Neurological	5,419	14,420	-9,001	-
Cutaneous	2,783	6,864	-4,081	-
Other non-pain	2,789	6,932	-4,144	-
HZ-related deaths	20	45	-25	-
Costs (discounted)				
Total direct costs	\$█	\$270,808,281	\$█	█
Vaccine acquisition	\$█	\$0	\$█	█
Vaccine administration	\$32,696,240	\$0	\$32,696,240	█
Vaccine-related AEs	\$6,218,093	\$0	\$6,218,093	█
HZ cases	\$13,789,427	\$42,047,738	-\$28,258,311	-█
PHN cases	\$37,488,142	\$107,712,207	-\$70,224,065	-█
Non-PHN complications cases	\$42,854,598	\$121,048,336	-\$78,193,738	-█
Outcomes (discounted)				
LYs	10,814,931	10,814,822	109	100.0%
QALYs	9,125,356	9,116,809	8,547	100.0%
Healthy QALYs lived	9,129,507	9,129,417	91	1.1%
Overall QALYs lost	4,152	12,608	-8,457	-98.9%
HZ	1,050	3,345	-2,295	-26.9%
PHN	3,101	9,263	-6,162	-72.1%
Vaccine-related AEs ^a	0	0	0	0.0%
Incremental cost per QALY gained			\$█ ¹	

Source: Table 3-51, pp202-203 of the resubmission.

AE = adverse event; HZ = herpes zoster; ICER = incremental cost-effectiveness ratio / cost per QALY; LY = life year; NNV = number needed to vaccinate; PHN = post-herpetic neuralgia; QALY = quality-adjusted life year; RZV = recombinant zoster vaccine (Shingrix).

^a Disutility applied to vaccine-related AE but overall impact small

The redacted values correspond to the following ranges:

¹ \$15,000 to < \$25,000

Public Summary Document – March 2023 PBAC Meeting

Table 13: Results of the economic evaluation for RZV vs no vaccine –Aboriginal and Torres Strait Islander adults ≥50 YOA

Result	RZV	No vaccine	Incremental difference	% of total difference
Case counts				
HZ cases	40,407	169,860	-129,453	-
PHN cases	6,790	27,601	-20,811	-
Non-PHN complications cases	4,394	17,330	-12,937	-
Ocular	1,693	6,688	-4,995	-
Neurological	1,459	5,566	-4,107	-
Cutaneous	579	2,374	-1,796	-
Other non-pain	663	2,702	-2,039	-
HZ-related deaths	2	5	-4	-
Costs (discounted)				
Total direct costs	\$█	\$99,069,423	\$█	█
Vaccine acquisition	\$█	\$0	\$█	█
Vaccine administration	\$32,696,240	\$0	\$32,696,240	█
Vaccine-related AEs	\$5,224,336	\$0	\$5,224,336	█
HZ cases	\$4,508,811	\$21,483,768	-\$16,974,957	-█
PHN cases	\$8,238,839	\$39,022,389	-\$30,783,549	-█
Non-PHN complications cases	\$8,418,724	\$38,563,266	-\$30,144,542	-█
Outcomes (discounted)				
LYs	7,520,562	7,520,549	14	100.0%
QALYs)	6,617,757	6,612,983	4,774	100.0%
Healthy QALYs lived	6,618,962	6,618,950	12	0.2%
Overall QALYs lost	1,205	5,967	-4,762	-99.8%
HZ	455	2,326	-1,870	-39.2%
PHN	749	3,641	-2,892	-60.6%
Vaccine-related AEs ^a	0	0	0	0.0%
Incremental cost per QALY gained			\$█ ¹	

Source: Table 3-55, p210 of the resubmission.

AE = adverse event; HZ = herpes zoster; ICER = incremental cost-effectiveness ratio / cost per QALY; LY = life year; NNV = number needed to vaccinate; PHN = post-herpetic neuralgia; QALY = quality-adjusted life year; RZV = recombinant zoster vaccine (Shingrix).

^a Disutility applied to vaccine-related AE but overall impact small

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

6.61 The results of the economic evaluation are sensitive to the following assumptions:

- The use of HZ incidence from MacIntyre (2015) which is likely to be overestimated, thus favouring RZV.
- The vaccine efficacy and the long-term waning of efficacy.
- The QALY loss assumed per case of HZ with and without PHN.
- The discount rate.

6.62 The base case ICER for the Aboriginal and Torres Strait Islander population (\$55,000 to < \$75,000/QALY) is higher than the ICER in the non-Indigenous population (\$15,000 to < \$25,000/QALY). The resubmission stated this may be because of the

lower life expectancy for the Aboriginal and Torres Strait Islander population compared to the non-Indigenous population, so they currently do not live long enough to accrue the complete benefits of vaccination. The ESC noted the ICER in the Aboriginal and Torres Strait Islander population if different mortality rates were applied significantly reduced the ICER which supports the interpretation that different mortality rates are having a significant impact on the cost-effectiveness of RZV.

6.63 The economic model results by different age cohorts is summarised in Table 14.

Table 14: Results of the economic evaluation for RZV vs no vaccine by age cohorts (NIP listing for shaded age groups not requested)

Result	50-59 YOA	60-64 YOA	65-69 YOA	70-79 YOA	≥80 YOA	Overall requested NIP population
Non-Indigenous population						
NNV to avoid one case of HZ	5	5	5	6	8	6
NNV to avoid one case of PHN	26	22	23	25	30	25
Incremental costs (\$)						
Incremental QALYs	5,631	8,163	8,616	8,687	8,215	8,547
Incremental cost per QALY gained (ICER) (\$)	█ ¹	█ ³	█ ³	█ ³	█ ³	█ ³
Aboriginal and Torres Strait Islander population						
NNV to avoid one case of HZ	7	7	10	22	21	8
NNV to avoid one case of PHN	43	44	58	97	79	49
Incremental costs (\$)						
Incremental QALYs	4,938	5,871	4,638	2,771	3,540	4,774
Incremental cost per QALY gained (ICER) (\$)	█ ²	█ ⁴	█ ²	█ ⁵	█ ²	█ ²

Source: Table 3-56 and 3-57, pp207-208 and pp214-215 of the resubmission.

HZ = herpes zoster; ICER = incremental cost-effectiveness ratio / cost per QALY; LY = life year; NNV = number needed to vaccinate; PHN = post-herpetic neuralgia; QALY = quality-adjusted life year; RZV = recombinant zoster vaccine (Shingrix).

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$55,000 to < \$75,000

³ \$15,000 to < \$25,000

⁴ \$35,000 to < \$45,000

⁵ \$95,000 to < \$115,000

6.64 The results of key univariate sensitivity analyses are summarised in Table 15 for non-Indigenous adults ≥65 YOA and in Table 16 for Aboriginal and Torres Strait Islander adults ≥50 YOA.

Public Summary Document – March 2023 PBAC Meeting

Table 15: Results of sensitivity analyses for RZV vs no vaccine, non-Indigenous adults > 65 YOA

Analyses	Incremental cost (discounted) (\$)	Incremental QALY (discounted)	ICER	% change to ICER
Base case		8,547		
Discount rate (base case 5% costs and outcomes) <ul style="list-style-type: none"> 0% costs and outcomes 1.5% costs and outcomes 3.5% costs and outcomes 		12,442 10,983 9,457		-64% -45% -20%
HZ Incidence (base case MacIntyre (2015)) <ul style="list-style-type: none"> MacIntyre (2015) + Qian (2021) Qian (2021) 		7,492 6,430		+29% +68%
Vaccine efficacy (base case ZOE-50 and ZOE-70) <ul style="list-style-type: none"> Izureita (2021) 		5,474		+113%
RZV waning (base case ZOE-50, ZOE-70, ZOSTER-49) <ul style="list-style-type: none"> Piecewise linear waning (UCI after 20 years) Alternate waning rate of 5.4% beginning at 10 years Alternate waning rate of 5.4% beginning at 15 years Upper limit from linear waning rate CI Lower limit from linear waning rate CI 		8,268 7,718 8,208 6,777 10,362		+7% +23% +9% +55% -37%
Healthcare resource utilisation (base case Karki, 2016 and Yawn, 2009) <ul style="list-style-type: none"> Yawn (2009) by age Yawn (2009) overall 		8,547 8,547		-26% +9%
Costs for hospitalisations (base case Brassel 2022) <ul style="list-style-type: none"> 2 x multiplier to cost of hospitalisation 0.5 x multiplier to cost of hospitalisation 		8,547 8,547		-73% +18%
Vaccination starting age (base case >65 YOA) <ul style="list-style-type: none"> >50 YOA 		7,478		+35%
2nd dose adherence (base case 80.3%) <ul style="list-style-type: none"> 78% 65% 		8,422 7,718		0% +3%
QALY loss (for HZ & HZ with PHN) (base case Gater 2014, Serpell 2014, Curran 2017) <ul style="list-style-type: none"> Upper 95% confidence interval Lower 95% confidence interval 		15,548 5,389		-45% +59%

Source: Table 3-63, p236 of the resubmission and compiled during the evaluation

HZ = herpes zoster; ICER = incremental cost-effectiveness ratio; PHN = post herpetic neuralgia; QALY = quality-adjusted life years; UCI = upper confidence interval

The redacted values correspond to the following ranges:

¹ \$15,000 to < \$25,000

² \$5,000 to < \$15,000

³ \$25,000 to < \$35,000

⁴ \$35,000 to < \$45,000

Table 16: Results of sensitivity analyses for RZV vs no vaccine, Aboriginal and Torres Strait Islander adults >50 YOA

Analyses	Incremental cost (discounted) (\$)	Incremental QALY (discounted)	ICER	% change to ICER
Base case		4,774	█ ¹	
Discount rate (base case 5% costs and outcomes) <ul style="list-style-type: none"> 0% costs and outcomes 1.5% costs and outcomes 3.5% costs and outcomes 	█	6,489 5,859 5,184	█ ² █ ² █ ³	-34% -24% -10%
HZ Incidence (base case BEACH (2006-2013)) <ul style="list-style-type: none"> MacIntyre (2015) + Qian (2021) Qian (2021) 	█	4,562 4,349	█ ¹ █ ¹	+6% +14%
Vaccine Efficacy (base case ZOE-50, ZOE-70) <ul style="list-style-type: none"> Izureita (2021) 	█	3,040	█ ⁴	+73%
RZV waning (base case ZOE-50, ZOE-70, ZOSTER-49) <ul style="list-style-type: none"> Piecewise linear waning (UCI after 20 years) Alternate waning rate of 5.4% beginning at 10 years Alternate waning rate of 5.4% beginning at 15 years Upper limit of linear waning rate CI Lower limit of linear waning rate CI 	█	4,639 4,451 4,667 4,138 5,316	█ ¹ █ ¹ █ ¹ █ ¹ █ ³	+4% +10% +3% +20% -13%
Costs for hospitalisations (base case Brassel (2022)) <ul style="list-style-type: none"> 2 x multiplier to cost of hospitalisation 0.5 x multiplier to cost of hospitalisation 	█	4,774 4,774	█ ³ █ ¹	-17% +5%
2nd dose adherence (base case 80.3%) <ul style="list-style-type: none"> 78% 65% 	█	4,726 4,457	█ ¹ █ ¹	0% -2%
QALY loss (for HZ & HZ with PHN) (base case Gater 2014, Serpell 2014, Curran 2017) <ul style="list-style-type: none"> Upper 95% confidence interval Lower 95% confidence interval 	█	10,575 2,581	█ ⁵ █ ⁴	-55% +85%

Source: Table 3-64, p236 of the resubmission.

Note: Lin data were only available for adults ≥ 60 YOA, the DSA low value is less favourable to the intervention than Lin data.

HZ = herpes zoster; ICER = incremental cost-effectiveness ratio; PHN = post herpetic neuralgia; QALY = quality-adjusted life years; UCI = upper confidence interval

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$35,000 to < \$45,000

³ \$45,000 to < \$55,000

⁴ \$95,000 to < \$115,000

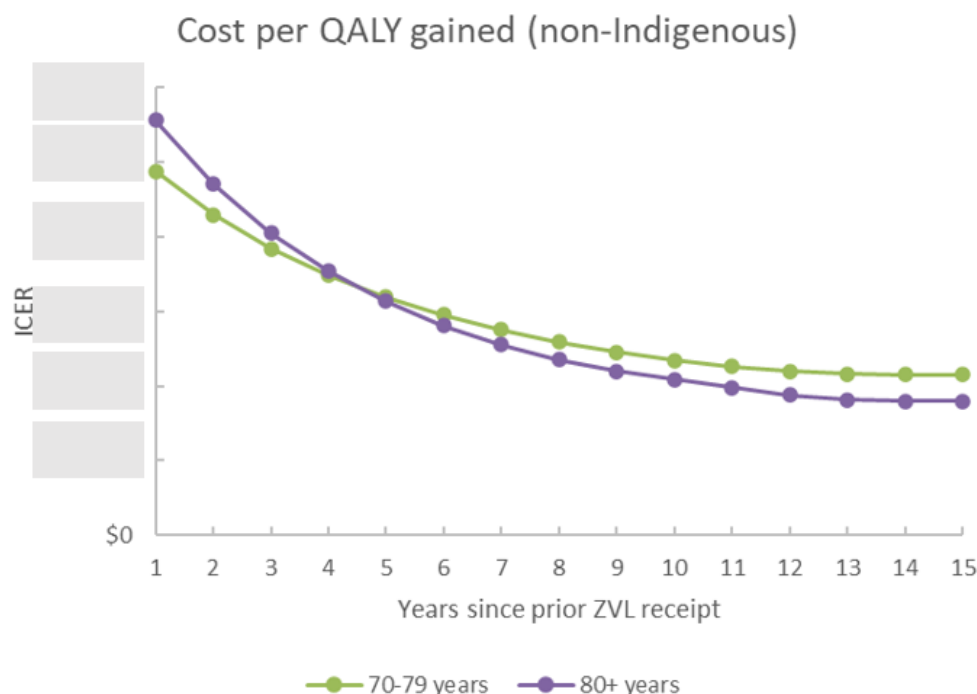
⁵ \$25,000 to < \$35,000

Supplementary analyses - RZV in people who have previously received ZVL

6.65 The resubmission presented results of an economic evaluation for RZV vaccination compared to no vaccine in adults who have previously received ZVL. At the ATAGI recommended interval of 5 years, the cost per QALY gained for RZV versus no vaccine was \$35,000 to < \$45,000 and \$35,000 to < \$45,000 for non-Indigenous adults 70-79 and ≥80 YOA (the population that would have received ZVL on the NIP), respectively. At the ATAGI recommended interval of 5 years, the cost per QALY gained for RZV versus no vaccine was \$155,000 to < \$255,000 and \$115,000 to < \$135,000 for Aboriginal and Torres Strait Islander adults 70-79 and ≥80 YOA, respectively. The ESC

noted the relationship between time since ZVL vaccination and cost effectiveness of RZV (Figure 3).

Figure 3: Cost per QALY gained by years since prior ZVL receipt



Source: Figure 3-26, page 217 of resubmission

Supplementary analyses – ZVL versus no vaccine in adults 70 – 79 YOA

6.66 The resubmission presented a secondary economic comparison of ZVL vs no vaccine in adults 70-79 YOA, to provide a benchmark for acceptable cost-effectiveness of HZ vaccines in the Australian setting. A price of \$█ was assumed in the base-case which resulted in an ICER of \$15,000 to < \$25,000/QALY. The resubmission stated this was the same as the ICER generated for RZV versus no vaccine in non-Indigenous adults ≥ 65 YOA. The resubmission stated the Department can input the true price of ZVL to generate more representative estimates of ZVL cost-effectiveness versus no vaccine. The secondary economic comparison using the confidential price of ZVL is presented in the CIC section in Section 7.

6.67 When recommending ZVL, the PBAC considered that a price reduction in the order of █% would be required to give an ICER in a range of \$15,000/QALY - \$45,000/QALY in the respecified base case (paragraph 6.27, Zostavax PSD, November 2014 PBAC meeting).

Vaccine cost/person/course

6.68 The cost of a course of RZV vaccination (2 doses) is \$█ per individual. This is lower than the cost of \$█ proposed in the 2018 submission.

Estimated PBS usage & financial implications

- 6.69 This resubmission was not considered by DUSC.
- 6.70 The resubmission used an epidemiological approach to estimate the utilisation and financial estimates of the proposed NIP listing of 2-dose RZV for non-Indigenous adults ≥ 65 YOA and Aboriginal and Torres Strait Islander adults ≥ 50 YOA. The proposed NIP listing also includes perpetual catch-up programs for both populations (as supported by ATAGI) and the financial estimates of these populations are included. The change in use and financial impact of ZVL were not included in the financial estimates as the resubmission assumed that ZVL will be discontinued in Australia in late 2023.
- 6.71 The key inputs and sources for the financial estimates are presented in Table 17.

Public Summary Document – March 2023 PBAC Meeting

Table 17: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Eligible population	Eligible population based on ABS data sources for all population groups. Aboriginal and Torres Strait Islander population projections based on “Estimates and Projections, Aboriginal and Torres Strait Islander Australians, 2006 to 2031 (Series 3238.0)”. Non-Indigenous projections based on “ABS Population Projections, Australia, 2017 (base), (Series 3222.0)”	These data sources are appropriate, and the approach used is reasonable.
Uptake rate: 1 st dose	Primary program: 1 st dose uptake rate of RZV ranged between 47% to 60% for non-Indigenous 65 YOA and 28% to 41% for Aboriginal and Torres Strait Islander adults 50 YOA. Cumulative coverage in the non-Indigenous primary program of people 65 YOA reached 75% and in the Aboriginal and Torres Strait Islander primary program of people 50 YOA reached 71%. Catch up program: 1 st dose uptake rate was assumed to cumulatively reach 65% by the sixth year of NIP listing.	Cumulative uptake rates were above the ATAGI recommended range of 50-65%. (ATAGI pre-submission advice to PBAC, November 2022).
Uptake rate: 2 nd dose	75% for 50-59 YOA	This aligns with ATAGI advice.
	80% for ≥60 YOA	This assumption does not align with ATAGI advice and is likely an overestimate. ATAGI advice recommended using a 65% to 78% for adherence with the recommended dosing schedule (ATAGI pre-submission advice to PBAC, November 2022). The PSCR stated the second dose uptake was based on post-marketing data for the 12 month 2 dose completion rates from the US and Canada. The PSCR noted the ATAGI advice was based on 2 to 6 month completion rates. The PSCR stated the 12 month completion was appropriate as vaccine effectiveness is not altered by receipt of the vaccine in this time frame.
HZ, PHN and non-PHN cases avoided	Results from the economic model used to determine cost saving to PBS (reduction in HZ related antivirals and PHN medications) and MBS (reduction in GP visits)	These estimates were reliant on several key assumptions made in the economic model. These include uncertainties in the use of incidence estimates, assumptions on extrapolation of vaccine efficacy (waning rates), and two-dose compliance.
Prior ZVL vaccination	Assumed that 30% of 70-79 YOA population had a prior ZVL vaccination. This estimate was based on NCIRS 2021.	The ATAGI post-submission advice provided data that supported a ZVL coverage of 43% in 70 to 74 YOA, 51% in 75 to 79 YOA and 28% in ≥ 80 YOA.
Prior HZ infection	Assumed that 30% of 70-79 YOA population had a prior HZ infection. Based on MacIntyre (2015)	Uncertain
Cost of vaccine administration	Level A consultation MBS item 3 = \$18.20	

Source: Table 4.2, pp239-241 of the resubmission, Table 4.3, p242 of the resubmission, Table 4.4, p242 of the resubmission, Table 4.5, p244 of the resubmission, Table 4.6, p244 of the resubmission, Table 4.7, pp244-245 of the resubmission, Table 4.8, p245 of the resubmission, Table 4.9, p245 of the resubmission, Table 4.10, pp245-246 of the resubmission and Table 4.11, p246 of the resubmission.

Public Summary Document – March 2023 PBAC Meeting

ABS = Australian Bureau of Statistics, HZ = herpes zoster, MBS = Medicare Benefits Schedule, NCIRS = National Centre for Immunisation Research & Surveillance, PHN = post-herpetic neuralgia, PSCR = pre-sub-committee response, RZV = recombinant zoster vaccine (Shingrix), YOA = years of age, ZVL = zoster vaccine live (Zostavax).

6.72 Table 18 summarises the overall estimated use and financial implications for the primary program for each of the proposed NIP populations.

Table 18: Estimated use and financial implications for the primary program

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of individuals vaccinated						
Aboriginal and Torres Strait Islander 50 YOA	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Non-Indigenous 65 YOA	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Number of doses dispensed						
Aboriginal and Torres Strait Islander 50 YOA	█ ¹	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷
Non-Indigenous 65 YOA	█ ³	█ ³	█ ⁹	█ ⁹	█ ⁹	█ ⁹
Estimated financial implications of RZV						
Aboriginal and Torres Strait Islander 50 YOA (\$)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Non-Indigenous 65 YOA (\$)	█ ⁵	█ ⁵	█ ⁸	█ ⁸	█ ⁸	█ ⁸
Estimated financial implications for PBS listed medicines						
Aboriginal and Torres Strait Islander 50 YOA (\$)	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Non-Indigenous 65 YOA (\$)	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Net financial implications						
Cost to NIP ^a (\$)	█ ⁵	█ ⁸	█ ⁸	█ ⁸	█ ⁸	█ ⁸
Net cost to PBS/RPBS (\$)	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Net cost to MBS (\$)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴

Source: Table 4.8, p.245 of the resubmission, Table 4.12, p.247 of the resubmission, Table 4.18, p.250 of the resubmission, Table 4.21, p.251 of the resubmission, Table 4.27, p.254 of the resubmission and Budget Impact Model Excel.

NIP = National Immunisation Program, MBS = Medicare Benefits Schedule, PBS = Pharmaceutical Benefit Scheme, RPBS = Repatriation Pharmaceutical Benefit Scheme, RZV = recombinant zoster vaccine (Shingrix)

^a No co-payments were required for any of the financial estimates

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 100,000 to < 200,000

³ 200,000 to < 300,000

⁴ \$0 to < \$10 million

⁵ \$40 million to < \$50 million

⁶ net cost saving

⁷ 5,000 to < 10,000

⁸ \$50 million to < \$60 million

⁹ 300,000 to < 400,000

6.73 Table 19 summarises the overall estimated use and financial implications for the catch-up program for each of the proposed NIP populations.

Public Summary Document – March 2023 PBAC Meeting

Table 19: Estimated use and financial implications for the catch-up programs

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of individuals vaccinated						
Aboriginal and Torres Strait Islander 50-69 YOA	1	15	20	23	23	20
Non-Indigenous 65-69 YOA	2	4	3	3	3	3
All 70-79 YOA, Prior ZVL	3	5	5	1	1	1
All 70-79 YOA, Prior HZ infection	3	5	5	1	1	1
All 70-79 YOA, Neither	4	3	21	24	24	24
All ≥80 YOA	4	3	3	25	25	25
Number of doses dispensed						
Aboriginal and Torres Strait Islander 50-69 YOA	5	1	15	20	20	20
Non-Indigenous 65-69 YOA	6	16	2	3	3	3
All 70-79 YOA, Prior ZVL	2	3	3	25	25	25
All 70-79 YOA, Prior HZ infection	2	3	3	25	25	25
All 70-79 YOA, Neither	2	4	3	26	26	26
All ≥80 YOA	6	2	4	3	3	3
Estimated financial implications to NIP of listing RZV						
Aboriginal and Torres Strait Islander 50-69 YOA (\$)	7	17	17	17	17	17
Non-Indigenous 65-69 YOA (\$)	8	18	9	14	14	14
All 70-79 YOA, Prior ZVL (\$)	9	7	7	17	17	17
All 70-79 YOA, Prior HZ infection (\$)	9	7	7	17	17	17
All 70-79 YOA, Neither (\$)	10	14	22	7	7	7
All ≥80 YOA (\$)	11	9	14	7	7	7
Estimated financial implications for PBS listed medicines						
Aboriginal and Torres Strait Islander 50-69 YOA (\$)	12	12	12	12	12	12
Non-Indigenous 65-69 YOA (\$)	12	12	12	12	12	12
All 70-79 YOA, Prior ZVL (\$)	12	12	12	12	12	12
All 70-79 YOA, Prior HZ infection (\$)	12	12	12	12	12	12
All 70-79 YOA, Neither (\$)	12	12	12	12	12	12
All ≥80 YOA (\$)	12	12	12	12	12	12
Net financial implications						
Cost to NIP (\$)	13	19	8	27	27	27
Net cost to PBS/RPBS (\$)	12	12	12	12	12	12
Net cost to MBS (\$)	14	7	7	17	17	17

Source: Table 4.9, p.245 of the resubmission, Table 4.13, p.247 of the resubmission, Table 4.19, p.250 of the resubmission, Table 4.22, p.251 of the resubmission, Table 4.28, pp.254-255 of the resubmission and Budget Impact Model Excel.

NIP = National Immunisation Program, MBS = Medicare Benefits Schedule, PBS = Pharmaceutical Benefit Scheme, RPBS = Repatriation Pharmaceutical Benefit Scheme, RZV = recombinant zoster vaccine (Shingrix)

The redacted values correspond to the following ranges:

- ¹ 30,000 to < 40,000
- ² 300,000 to < 400,000
- ³ 100,000 to < 200,000
- ⁴ 200,000 to < 300,000
- ⁵ 60,000 to < 70,000
- ⁶ 500,000 to < 600,000
- ⁷ \$10 million to < \$20 million

Public Summary Document – March 2023 PBAC Meeting

- ⁸ \$100 million to < \$200 million
- ⁹ \$50 million to < \$60 million
- ¹⁰ \$60 million to < \$70 million
- ¹¹ \$90 million to < \$100 million
- ¹² net cost saving
- ¹³ \$300 million to < \$400 million
- ¹⁴ \$30 million to < \$40 million
- ¹⁵ 20,000 to < 30,000
- ¹⁶ 400,000 to < 500,000
- ¹⁷ \$0 to < \$10 million
- ¹⁸ \$70 million to < \$80 million
- ¹⁹ \$200 million to < \$300 million
- ²⁰ 10,000 to < 20,000
- ²¹ 80,000 to < 90,000
- ²² \$20 million to < \$30 million
- ²³ 5,000 to < 10,000
- ²⁴ 40,000 to < 50,000
- ²⁵ 50,000 to < 60,000
- ²⁶ 70,000 to < 80,000
- ²⁷ \$80 million to < \$90 million

6.74 Table 20 shows the overall estimated use and financial implications for both primary and catch-up programs.

Table 20: Estimated net financial implications for both primary and catch-up programs

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total doses	1	1	1	9	9	9
Cost to NIP (\$)	2	5	5	8	8	8
Net cost to PBS/RPBS (\$)	3	3	3	3	3	3
Net cost to MBS (\$)	4	6	7	7	7	10
Previous submission November, 2018						
Net cost to NIP (\$)	2	5	8	8	8	11
Net cost to PBS/RPBS (\$)	3	3	3	3	3	3
Net cost to MBS (\$)	3	3	3	3	3	3

Source: Table 4.27, pp.254 of the resubmission, Table 4.28, pp.254-255 of the resubmission and Budget Impact Model Excel.

NIP = National Immunisation Program, MBS = Medicare Benefits Schedule, PBS = Pharmaceutical Benefit Scheme, RPBS = Repatriation Pharmaceutical Benefit Scheme

Blue shading indicates information previously considered by the PBAC (2018 submission). Note that the proposed NIP population considered in the 2018 submission is adults ≥60 YOA.

The redacted values correspond to the following ranges:

- ¹ 1,000,000 to < 2,000,000
- ² \$400 million to < \$500 million
- ³ net cost saving
- ⁴ \$40 million to < \$50 million⁵ \$200 million to < \$300 million
- ⁶ \$20 million to < \$30 million
- ⁷ \$10 million to < \$20 million
- ⁸ \$100 million to < \$200 million
- ⁹ 800,000 to < 900,000
- ¹⁰ \$0 to < \$10 million
- ¹¹ \$80 million to < \$90 million

6.75 The cost to the NIP for listing RZV for the primary program is estimated to be \$40 million to < \$50 million in the first year, increasing to approximately \$50 million to < \$60 million at Year 6, totalling \$300 million to < \$400 million over 6 years. For the catch-up program, it is estimated to be \$300 million to < \$400 million in the first year, decreasing to approximately \$80 million to < \$90 million at Year 6, totalling > \$1 billion over 6 years.

Public Summary Document – March 2023 PBAC Meeting

- 6.76 The ESC noted the financial estimates did not exclude people who had received ZVL in the last 5 years or account for people who had been previously vaccinated with RZV. The ESC considered that, given the likely duration of effect of RZV, it may be reasonable to exclude these people from being revaccinated on the NIP. The ESC indicated that ATAGI advice on this issue would be informative. The ATAGI post-submission advice stated it is reasonable and implementable to limit the use of RZV in people who (i) have received ZVL within the last 5 years and (ii) have received 2 doses of RZV. The ATAGI considered it was reasonable to limit individuals who have already received one dose of RZV to receiving one dose on the NIP.
- 6.77 The ESC noted that, based on the estimates provided in the resubmission, of the > \$1 billion cost of including RZV on the NIP over 6 years, \$600 million to < \$700 million (51%) was in people aged 50 to 69 YOA, \$400 million to < \$500 million (31%) was in people aged 70 to 79 YOA and \$200 million to < \$300 million (17%) was in people aged ≥80 YOA. The ESC noted excluding the 30% of people aged 70-79 YOA who have received ZVL would reduce the cost by \$100 million to < \$200 million over 6 years.
- 6.78 The resubmission anticipated a reduction in the use of medications used to treat HZ, PHN and non-PHN complications that will result in PBS savings of a total of \$0 to < \$10 million over 6 years for the primary program and \$20 million to < \$30 million over 6 years for the catch-up programs. These estimates may be overestimated as they were based on estimated reductions in the incidence of HZ, PHN, and non-PHN complications from the economic model.
- 6.79 Across both the primary and catch-up programs, the total cost to MBS would range from \$40 million to < \$50 million in Year 1 to \$0 to < \$10 million in Year 6, totalling \$100 million to < \$200 million over 6 years. These estimates are uncertain given the reliance on the outputs from the economic model and the assumptions made. Across both primary and catch-up programs, the total GP cost offset is estimated to be \$20 million to < \$30 million, while the total vaccine administration cost is estimated to be \$100 million to < \$200 million.
- 6.80 The resubmission identified the 1st dose coverage and 2nd dose compliance as the key sources of uncertainty. Increasing or decreasing the first dose coverage by 10 percentage points resulted in a 18.4% increase or decrease in the overall net cost over six years. Increasing or decreasing the 2nd dose compliance by 10 percentage points resulted in a 5.8% increase or decrease in the overall net cost over 6 years.
- 6.81 The resubmission also provided financial estimates for the proposed optional population of immunocompromised adults ≥18 YOA. The resubmission used self-reported immunosuppressed status in the US (Harpaz, 2016) to calculate the number of immunosuppressed people and assumed a 65% uptake. The resubmission estimated the number of immunocompromised adults in Year 1 would be 400,000 to < 500,000 with 200,000 to < 300,000 expected to be vaccinated. In the Harpaz study, people reporting immunosuppressive medications or treatments or

occurrence of immunosuppressive medical conditions (i.e., hematopoietic cancers or HIV infection) were considered immunosuppressed. Those reporting only frequent colds or infections or attributing immunosuppression solely to chronic diseases or to solid cancers (i.e., in absence of immunosuppressive treatments) were not considered to be immunocompromised.

- 6.82 The resubmission stated that these were provided as an indicative estimate as to the size and potential financial impact of RZV in these populations based on prevalence data reported by ATAGI.
- 6.83 The estimated cost of RZV to the NIP for immunocompromised adults ≥ 18 YOA was \$80 million to < \$90 million in Year 1, decreasing to approximately \$0 to < \$10 million at Year 6, totalling \$100 million to < \$200 million over 6 years. These estimates do not include the cost of administration (only vaccine costs are reflected).
- 6.84 These estimates represent the cost of RZV to the NIP for populations for whom no cost-effectiveness analysis was presented in the resubmission : immunocompromised non-Indigenous adults 18 to 64 YOA and immunocompromised Aboriginal and Torres Strait Islander adults 18 to 49 YOA. These estimates should be interpreted with caution because of uncertainty with respect to the definition of immunocompromised and the age threshold at which these populations may be eligible for RZV. The source used to estimate age-specific prevalence of immunosuppressed persons may not be reflective of the Australian population. The ESC considered it was unclear if the approach in the resubmission accurately represents the Australian population of immunocompromised people who would most benefit from receiving RZV. The ESC indicated that further ATAGI advice on this issue would be informative.
- 6.85 The ATAGI post-submission advice estimated there are 126,170 individuals over 18 years of age with conditions at high risk of HZ defined as haematopoietic stem cell transplant, solid organ transplant recipients on immunosuppressive therapy, active haematological malignancies and advanced or untreated HIV with CD4 counts $< 250/\mu\text{L}$ or those with a higher CD4 count unable to be established on effective anti-retroviral therapy.
- 6.86 The ATAGI post-submission advice estimated there are 464,697 individuals over 18 years of age with conditions at moderate risk of HZ defined as rheumatoid arthritis and systemic lupus erythematosus.
- 6.87 The PBAC noted the ATAGI pre-submission advice stated that people on one or more immunosuppressive therapies (high dose systemic corticosteroids, DMARDs, chemotherapy/ radiotherapy) are at high risk of HZ, regardless of the underlying condition. The PBAC considered there is likely to be individuals with low or moderate risk conditions on these immunosuppressive treatments that would be at similar (or higher) risk of HZ than the individuals identified in paragraph 6.85; however, this population has not been defined. Additionally, the PBAC noted the consumer comments specifically discussed individuals with multiple sclerosis on immunosuppressive treatments and those on JAK inhibitors as being at high risk of HZ.

- 6.88 The PBAC recalled a report on the risk of HZ infection in patients taking biologics and JAK inhibitor medicines for autoimmune conditions considered at the December 2022 PBAC meeting which indicated patients at most risk of HZ infection were those taking JAK inhibitors with rheumatoid arthritis or inflammatory bowel disease³.

Quality Use of Medicines

- 6.89 The resubmission indicated that ongoing educational support and materials, including working with jurisdictions and supporting and sponsoring immunisation provider educational initiatives will continue.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended that varicella virus recombinant vaccine (RZV, Shingrix) be a designated vaccine for the purposes of the National Health Act 1953, for the prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN). The PBAC considered the range of incremental cost effectiveness ratios (ICERs) presented in the resubmission were acceptable at the price requested in the resubmission (\$█ per dose) for non-Indigenous individuals aged 70 years, Aboriginal and Torres Strait Islander individuals aged ≥ 50 years and immunocompromised individuals aged ≥ 18 years with conditions at high risk of HZ infection (as defined by ATAGI).
- 7.2 The PBAC deferred a decision for the broader population of immunocompromised individuals aged ≥ 18 years at increased risk of HZ infection to seek further ATAGI advice on the appropriate definition of this population. VZ
- 7.3 The PBAC did not recommend RZV for non-Indigenous individuals aged 65 to 69 years and individuals aged ≥ 71 years. The PBAC noted that these populations were of lower clinical priority and represented a high volume of doses (5,000,000 to < 6,000,000 doses over 6 years with an associated cost of \$900 million to < \$1 billion). In the context of the total cost, the PBAC considered the extent of uncertainty regarding the cost-effectiveness of RZV to be too high.
- 7.4 The PBAC noted the consumer comments were highly supportive of including RZV on the NIP. The PBAC noted the burden of HZ and its complications and the importance of having a safe and effective vaccine available that can be used in immunocompromised individuals. The PBAC noted a number of comments raised the equity issues associated with the high cost of RZV on the private market.
- 7.5 The PBAC noted the resubmission requested inclusion on the NIP for non-Indigenous individuals aged 65 years with an ongoing catch up program for people aged 66 years and over and for Aboriginal and Torres Strait Islander individuals aged 50 years with

³ <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/recommendations-made-by-the-pbac-december-2022-intracycle>

an ongoing catch up program for people aged 51 years and over.

- 7.6 The PBAC noted that while immunocompromised individuals who meet the age criteria in paragraph 7.5 would be eligible for RZV, the resubmission did not present an economic evaluation for younger immunocompromised individuals (i.e., non-Indigenous people aged 18 to 64 years or Aboriginal and Torres Strait Islander people aged 18 to 49 years). Rather, the resubmission stated that it could be assumed that the cost effectiveness of RZV in the requested NIP population would be applicable to the immunocompromised population at a younger age threshold with similar or greater risk of HZ, and similar efficacy, immunogenicity, and safety of RZV.
- 7.7 The PBAC noted a live zoster vaccine (ZVL, Zostavax) is currently listed on the NIP for individuals aged 70 years with a catch up program in place for individuals aged at least 71 years and less than 80 years of age until 31 October 2023. The PBAC noted the resubmission assumed that the supply of ZVL to the NIP will cease “from late 2023” and, based on this assumption, the resubmission nominated no vaccine (placebo) as the comparator for all requested populations.
- 7.8 The PBAC noted that, in addition to the two studies previously considered by the PBAC (ZOE-50 and ZOE-70), the resubmission presented data from ZOSTER-049, a long-term follow-up study of ZOE-50 and ZOE-70 participants. The PBAC noted the clinical claim in the resubmission was that RZV is superior in terms of effectiveness compared with placebo and slightly inferior in terms of safety compared to placebo for the proposed NIP populations described in paragraph 7.5. The PBAC considered this claim was reasonable, consistent with its previous consideration (paragraph 7.4, RZV PSD, November 2018 PBAC meeting).
- 7.9 The PBAC noted the vaccine efficacy against HZ (VE_{HZ}) for individuals who received two doses was high (90% to 97%, see Table 5) and while VE_{HZ} appeared to be reducing over time, it remained high (84%) after 8 years. The PBAC noted some data for VE_{HZ} for individuals receiving one dose was available (see paragraph 6.48 and 6.53) but considered that, overall, the effectiveness of one dose remained uncertain.
- 7.10 The PBAC noted individuals who had previously received ZVL, previously had HZ or were immunocompromised were excluded from the ZOE-50 and ZOE-70 studies. The resubmission presented a number of supportive studies to support the effectiveness and safety of RZV in these populations. The PBAC noted ATAGI advice that the evidence presented supported the safety, immunogenicity and efficacy of RZV in the populations that were excluded from the ZOE studies but the PBAC considered VE_{HZ} may be lower in these individuals.
- 7.11 The PBAC noted the base case ICER for the non-Indigenous population was \$15,000 to < \$25,000/QALY and it was reasonably consistent across the different age groups (\$15,000 to < \$25,000/QALY to \$15,000 to < \$25,000/QALY, see Table 14). The PBAC noted that applying a discount rate of 3.5% to costs and outcomes decreased the ICERs by approximately 20%.

- 7.12 The PBAC noted the base case ICER in the Aboriginal and Torres Strait Islander population was \$55,000 to < \$75,000/QALY which was higher than in the non-Indigenous population. The PBAC noted while there is limited data available on the incidence of HZ and PHN in the Aboriginal and Torres Strait Islander population, the age-specific rates of HZ-related hospitalisation were generally higher than for the non-Indigenous population, which suggests a higher disease burden. The PBAC noted the higher ICER reflected the lower life expectancy reported for the Aboriginal and Torres Strait Islander population.
- 7.13 The PBAC noted the cost effectiveness of RZV was not assessed in immunocompromised individuals but considered that, for the population with conditions at high risk of HZ infection and complications (as described in paragraph 6.85), RZV was likely to be at least similarly cost-effective.

Recommendation for non-Indigenous individuals aged 70 years, Aboriginal and Torres Strait Islander individuals aged ≥ 50 years and immunocompromised individuals aged ≥ 18 years with conditions at high risk of HZ infection

- 7.14 The PBAC recommended RZV be a designated vaccine for the purposes of *the National Health Act 1953*, for the prevention of herpes zoster (HZ) and post-herpetic neuralgia for non-Indigenous individuals aged 70 years, Aboriginal and Torres Strait Islander individuals aged ≥ 50 years and immunocompromised individuals aged ≥ 18 years with conditions at high risk of HZ infection.
- 7.15 The PBAC considered the range of ICERs presented in the resubmission were acceptable at the price requested for these populations, noting the high clinical priority due to the potential loss of the ZVL through the NIP and the high risk of HZ infection and complications. The PBAC noted that the cost-effectiveness of RZV relied on its efficacy being maintained well beyond the 10 years for which clinical data are available. In this context, the PBAC considered the long-term efficacy of RZV should be monitored and the cost-effectiveness reconsidered if a booster dose is required or if long-term efficacy is less than predicted (see Figure 2).
- 7.16 The PBAC noted that a booster dose with RZV is not currently recommended and therefore at this stage individuals previously vaccinated with 2 doses of RZV should not be eligible for RZV through the NIP. The PBAC noted the ICERs for individuals who have previously received ZVL were higher than the base case ICERs (see paragraph 6.65). However, the PBAC considered that, given the effectiveness of ZVL was likely to be low after 5 years, vaccination with RZV after this timeframe would be clinically reasonable as supported by ATAGI (see paragraph 6.76) and should be funded on the NIP.
- 7.17 The PBAC considered the estimated financial cost of listing RZV on the NIP for non-Indigenous individuals aged 70 years, Aboriginal and Torres Strait Islander individuals aged ≥ 50 years and immunocompromised individuals aged ≥ 18 years with conditions at high risk of HZ infection could reliably be determined using the estimates model provided in the resubmission (with appropriate amendments to account for a primary

program in individuals aged 70 years, rather than 65 years). The PBAC noted individuals previously vaccinated with 2 doses of RZV and individuals who have received ZVL in the previous 5 years should be removed from the estimates. The PBAC noted the ATAGI post-submission advice estimated the prevalence of immunocompromised individuals aged ≥ 18 years with conditions at the high risk of HZ (as defined in paragraph 6.85) is 126,170.

Recommendation for the broader population of immunocompromised individuals aged ≥ 18 years at increased risk of HZ

- 7.18 The PBAC deferred a decision for the broader population of immunocompromised individuals aged ≥ 18 years at increased risk of HZ infection.
- 7.19 The PBAC considered there was likely to be a broader population of immunocompromised individuals aged ≥ 18 years at increased risk of HZ for whom RZV was similarly cost effective to the populations identified in paragraph 7.14, but this population had not yet been clearly defined (as discussed in paragraph 6.87). The PBAC deferred a recommendation to seek further ATAGI advice on the broader immunocompromised population for whom RZV would be appropriate. The PBAC requested that the sponsor provide information to support the cost-effectiveness in the population as defined by ATAGI, noting that it would likely be based on the incidence of HZ and associated complications compared with the recommended populations. Additionally, the PBAC requested that the sponsor provide financial estimates of including RZV on the NIP for this population, noting individuals previously vaccinated with 2 doses of RZV should be removed from the estimates.

Recommendation for non-Indigenous individuals aged 65 to 69 years and ≥ 71 years

- 7.20 The PBAC did not recommend RZV for non-Indigenous individuals aged 65 to 69 years and ≥ 71 years.
- 7.21 The PBAC considered a price reduction would be required for RZV to be cost-effective for these populations, noting that they were of lower clinical priority and represented a high volume of doses (5,000,000 to $< 6,000,000$ doses over 6 years with an associated cost of \$900 million to $< \$1$ billion). In the context of the total cost, the PBAC considered the extent of uncertainty regarding the cost-effectiveness of RZV to be too high. Specifically the PBAC noted:
- The ICER was sensitive to the incidence of HZ. The PBAC noted the ATAGI post-submission advice that the best estimate of incidence was a pooled estimate using data from MacIntyre 2015, Qian 2021a and Lin 2022. The PBAC noted that this scenario was not included in the resubmission and the PSCR and pre-PBAC response considered it appropriate for Lin 2022 to be excluded as it would significantly underestimate the incidence of HZ due to methodological issues. The PBAC noted the ICER increased to \$25,000 to $< \$35,000$ /QALY using pooled data from MacIntyre and Qian and to \$25,000 to $< \$35,000$ /QALY using Qian alone.
 - The ICER was sensitive to the VE estimates. The PBAC noted the ATAGI post-

submission advice that the V_{Eff} for two doses from Izurieta 2021 could be used in sensitivity analyses, and that use of this estimate increased the ICER to \$35,000 to < \$45,000/QALY.

- The ICER was sensitive to assumptions regarding long-term waning of efficacy, and the PBAC noted for the base case analysis the VE remained above 50% for more than 20 years. The PBAC noted the resubmission presented a scenario analysis in which the upper confidence interval for the waning function was applied after 20 years, however considered this scenario did not adequately address the uncertainty given clinical data were available for only up to 10 years. The PBAC noted the ICER increased to \$25,000 to < \$35,000/QALY if an annual waning rate of 5.4% was assumed from 10 years after vaccination. The PBAC also noted the waning assumptions become more critical when vaccinating a younger cohort.
- The ICER was sensitive to the assumed QALY loss per HZ and PHN event and the ESC considered the QALY loss per case of HZ and PHN were overestimated given the trial data demonstrated attenuation of disease impact over the period of HZ. The PBAC noted the ICER increased to \$25,000 to < \$35,000/QALY when the lower 95% confidence intervals were used to inform the QALY loss per event.

7.22 The PBAC noted the resubmission presented a secondary economic comparison of ZVL vs no vaccine in adults aged 70-79 years, to provide a benchmark for acceptable cost-effectiveness of HZ vaccines in the Australian setting. The PBAC noted this analysis supported a threshold ICER of \$15,000 to < \$25,000/QALY if the price of ZVL is \$█ per dose.

Start committee – in-confidence

7.23 The PBAC noted the ICER for the secondary comparison using the current price of ZVL ████. The PBAC noted the ICER accepted for ZVL was █, and that the █ ICER using the model included in the current submission suggested ████.

End committee-in-confidence

7.24 The PBAC did not consider RZV was cost-effective for non-Indigenous individuals aged 65 to 69 years and ≥ 71 years. The PBAC recalled its November 2018 advice for RZV that given the large opportunity cost, more conservative cost-effectiveness analyses were required (paragraph 7.1, RZV PSD, November 2018 PBAC meeting). The PBAC maintained this advice and considered that any resubmission should present additional cost effectiveness analyses including univariate and multivariate analyses addressing the issues outlined in paragraph 7.21.

7.25 The PBAC considered the estimated financial cost of listing RZV on the NIP for non-Indigenous individuals aged 65 to 69 years and ≥ 71 years could reliably be determined using the estimates model provided in the resubmission. The PBAC noted in any resubmission individuals previously vaccinated with 2 doses of RZV and individuals who have received ZVL in the previous 5 years should be removed from the estimates. The PBAC noted the ATAGI post-submission advice indicated the proportion of the

population that has previously received ZVL was higher than assumed in the resubmission (see Table 17).

7.26 The PBAC considered the outstanding issues for non-Indigenous individuals aged 65 to 69 years and ≥ 71 years could be easily resolved in a simple resubmission for RZV using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:

- Present additional cost-effectiveness analyses as outlined in paragraph 7.24; and
- Provide revised financials as outlined in paragraph 7.25.

The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.27 The PBAC noted that this submission is not eligible for an independent review as independent review is only relevant to requests for PBS listing

Outcome:

Recommended for non-Indigenous individuals aged 70 years, Aboriginal and Torres Strait Islander individuals aged ≥ 50 years and immunocompromised individuals aged ≥ 18 years with conditions at ‘high risk’ of HZ infection.

Deferred for the broader population of immunocompromised individuals aged ≥ 18 years at increased risk of HZ infection, with further advice being sought from ATAGI.

Not recommend for non-Indigenous individuals aged 65 to 69 years and ≥ 71 years.

8 Recommended listing

8.1 Add new item to the Determination:

Vaccine and the circumstances in which vaccine may be provided	Brand	Formulation	Number and timing of doses
recombinant varicella zoster virus glycoprotein E antigen (AS01 _B Adjuvanted) vaccine	Shingrix	powder and suspension for injection, 0.5 mL	a. Two primary doses 2 to 6 months apart b. For subjects who are immunodeficient, immunosuppressed or likely to become immunosuppressed due to known disease or therapy, two primary doses can be given 1 to 2 months apart c. Those eligible populations who have received one dose privately can receive their second dose on the NIP

Circumstances

Vaccine may be provided to a person who:

- (a) turns 70 years of age on or after [date of inclusion on NIP]; or

Public Summary Document – March 2023 PBAC Meeting

- (b) is an Aboriginal and Torres Strait Islander individual who is at least 50 years of age as of [date of inclusion on NIP]; or
- (c) who is at least 18 years of age as of [date of inclusion on NIP] and:
 - i. has had a haemopoietic stem cell transplantation or is scheduled to receive a haemopoietic stem cell transplantation or
 - ii. has had a solid organ transplant or is scheduled for a transplant and is on immunosuppressive therapy or
 - iii. has an active haematological malignancy or
 - iv. has advanced or untreated HIV with CD4 counts < 250/ μ L or those with a higher CD4 count unable to be established on effective anti-retroviral therapy.

The wording of the item may be subject to further review. Should there be any changes made to the item the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

GSK welcomes the Pharmaceutical Benefits Advisory Committee (PBAC) decision to recommend the listing of Shingrix on the National Immunisation Program (NIP) for: non-Indigenous adults 70 years of age at the time of the first dose; Aboriginal and Torres Strait Islander adults 50 years of age and older; and immunocompromised adults 18 years of age and above at high increased risk of herpes zoster (as defined for the NIP by the Australian Technical Advisory Group on Immunisation, ATAGI).

ATAGI is supportive of access to Shingrix for the wider community beyond the groups recommended. GSK acknowledges the numerous consumer comments from organisations and individuals supporting a broad NIP listing of Shingrix, however not all patient groups that they serve will be eligible for funded Shingrix on the NIP within the currently recommended cohorts. GSK will continue to partner with the PBAC to explore opportunities to expand access to the vaccine.