

5.17 RECOMBINANT VARICELLA ZOSTER VIRUS VACCINE, Injection [1 vial] & adjuvant substance diluent [0.5 mL vial], Shingrix®, GlaxoSmithKline

1 Purpose of Application

- 1.1 National Immunisation Program (NIP) listing for the recombinant varicella zoster virus glycoprotein E antigen (AS01_B adjuvanted) vaccine (hereafter referred to as the HZ/su vaccine) at 60 years (with a five-year catch-up program), for the prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN). The PBAC has not previously considered this vaccine.
- 1.2 In November 2014 the PBAC recommended listing vaccination of immunocompetent individuals aged 70 years with the zoster virus vaccine live (live-HZ), with a five-year catch-up program for immunocompetent individuals aged 70-79 years.
- 1.3 The requested basis for listing HZ/su was cost-effectiveness compared to no vaccine and the live-HZ vaccine.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adults aged 60 years old and older.
Intervention	Recombinant Varicella Zoster Virus glycoprotein E antigen (AS01 _B adjuvanted) vaccine (Shingrix®)
Comparator	60-69 year olds: No vaccine 70-79 year olds: Live herpes zoster (live-HZ) vaccine (Zostavax®) 80+ year olds: No vaccine
Outcomes	Cases of HZ Cases of post-herpetic neuralgia HZ-associated complications HZ-related mortality and hospitalisations HZ-associated pain Vaccine immunogenicity Vaccine safety and reactogenicity.
Clinical claim	In 70-79 year olds, the HZ/su vaccine administered as a two-dose vaccine provides superior efficacy and a similar safety profile but is more reactogenic compared with the live-HZ vaccine. In 60-69 and 80+ year olds, the HZ/su vaccine administered as a two-dose vaccine provides superior efficacy and slightly inferior safety compared with no vaccine.

HZ: herpes zoster

Source: Compiled during the evaluation based on p26, p66 and p100 of the submission

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

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
RECOMBINANT VARICELLA ZOSTER VIRUS GLYCOPROTEIN E ANTIGEN (AS01b ADJUVANTED) VACCINE Powder and suspension for injection, 0.5 mL	NS	NS	NS	Shingrix® GlaxoSmithKline
Category/Program:	National Immunisation Program			

NS: not specified.

Source: Table 1, p18 of the submission and compiled during the evaluation.

2.1 The submission proposed the following administration schedule.

Table 2: Requested NIP listing

Age at time of first injection	Immunisation and schedule	Duration of NIP listing
60 years	Two doses each of 0.5 mL; The second dose given two months to six months after the first dose.	Ongoing NIP cohort
60-69 years		5 year catch-up
70-79 years		
80 years and over		

Source: Table 3, p27 of the vaccine.

2.2 The requested NIP listing for those aged 60, with a five-year catch-up program, is a sub-set of the TGA indication, which is for individuals aged 50 years and older. The PBAC noted that the requested NIP listing did not include the ATAGI recommended populations of individuals aged 50 years and over who are: (i) immunocompromised or immunosuppressed who cannot receive the live-HZ vaccine; or (ii) Aboriginal or Torres Strait Islander, who have a greater burden of disease.

2.3 The ESC noted that the key clinical trials excluded individuals who:

- had previously received the live-HZ vaccine.
- had previously had HZ.
- were immunosuppressed or immunocompromised.

2.4 The Pre-Sub-Committee Response (PSCR) noted that the approved Australian Product Information for the HZ/su vaccine does not exclude vaccination of adults over 50 years of age who have previously received a varicella/HZ vaccine, have had a previous history of HZ or who are immunocompromised or immunosuppressed. In addition, the PSCR stated that a number of studies demonstrated vaccine efficacy and acceptable safety in these patient groups. The ESC considered this informative but noted that although immunocompromised patients were at higher risk of HZ, adjusting for this risk in the economic and financial estimates may have resulted in an overestimate of HZ and PHN events avoided. The pre-PBAC Response argued that immunocompromised or immunosuppressed patients make up less than 2% of the adult population¹; therefore, considered that any impact on the economic evaluation

¹ Varghese L, Curran D, Bunge E, et al. Contraindication of live vaccines in immunocompromised patients: an

would be minimal. The PBAC considered this number might be higher given the increasing number of patients on immunotherapies.

- 2.5 The financial estimates were not consistent with the requested NIP listing. The financial impact estimates included individuals receiving vaccinations in Year 6 at 70 years and 80 years across the forward estimates. After the five-year catch-up the ongoing NIP cohort will be for individuals aged 60 years only. Also, the inclusion of 70 year old and 80 year old programs as well as catch up cohorts may have double counted some individuals. The pre-PBAC Response stated that the separate costs for the 60, 70 and 80 year old cohorts (together with separate catch-up programs for 61-69, 71-79 and 81 year olds, respectively) was so that the PBAC could assess the potential cost to Government for each age cohort.

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

3 Background

Registration status

- 3.1 The HZ/su vaccine was recommended for registration by the TGA delegate on 28 June 2018 for the prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in adults 50 years of age or older.

Previous considerations

- 3.2 In November 2014 the PBAC recommended listing zoster virus vaccine live (live-HZ) on the NIP for immunocompetent persons aged 70 years, with a catch-up cohort of persons aged 71 to 79 years.

4 Population and disease

- 4.1 Primary varicella zoster virus infection results in varicella (or chickenpox), after which the virus becomes latent in neurons of dorsal root and cranial nerve ganglia. HZ (or shingles) results from the reactivation of latent varicella zoster virus in sensory ganglia. Symptoms include: pain, itching, numbness or tingling (paraesthesias), unpleasant sensations (dysaesthesias) or sensitivity to touch (allodynia) in one to three dermatomes; malaise, headache and fever; unilateral maculopapular rash; and acute pain typically lasting 10 to 15 days.
- 4.2 The key complication of HZ is PHN, which is defined as a pain score of least three on the Zoster Brief Pain Inventory (ZBPI) scale persisting for longer than 90 days.

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

5 Comparator

- 5.1 The submission nominated the following comparators:
- Individuals aged 60-69 year olds: no vaccine
 - Individuals aged 70-79 year olds: live-HZ vaccine
 - Individuals aged 80+ year olds: no vaccine
- 5.2 The main arguments provided in support of this nomination were that the live-HZ vaccine is currently listed on the NIP for adults aged 70+ years. A single dose is listed for 70 year olds, with a single catch-up dose for adults aged 71-79 years until 31 October 2021.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 The submission was based on two randomised trials:
- ZOE-50: Compared two doses of the HZ/su vaccine to placebo in adults aged 50 years and over (N=15,411)
 - ZOE-70: Compared two doses of the HZ/su vaccine to placebo in adults aged 70 years and over (N=13,900)
- 6.4 The submission also presented an indirect comparison of the HZ/su vaccine to the live-HZ vaccine, using placebo as the common comparator, based on the following:
- Pooled analysis of ZOE-50 and ZOE-70: Compared two doses of the HZ/su vaccine to placebo in adults aged 70 years and over (N=16,596)
 - SPS trial: Compared the live-HZ vaccine to placebo in adults aged 60 years and over (N=38,546).
- 6.5 Details of the trials presented in the submission are provided in Table 3.

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Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ZOE-50 (ZOSTER-006, study 110390, NCT01165177)	A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01B vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older, clinical study report Lal 2015, Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults.	18 May 2016 <i>NEJM</i> 2015; 372, 2087-2096
ZOE-70 (ZOSTER-022, study 113077, NCT01165229)	A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety and immunogenicity of GSK Biologicals' gE/AS01B vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 70 years and older Cunningham 2016, Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. McElhane 2016, Efficacy, Immunogenicity and Safety of an Investigational Subunit Adjuvanted Herpes Zoster Vaccine in Adults Aged 60 Years and Older: Results from the ZOE-50 and ZOE-70 Efficacy Studies	18 May 2016 <i>NEJM</i> 2016; 375, 1019-1032. <i>Oral abstract. Conference not reported.</i>
SPS	Oxman 2005, A vaccine to prevent herpes zoster and post herpetic neuralgia in older adults. 2005; <i>N Engl J Med</i> , 352, 2271-84. Zostavax FDA report	<i>NEJM</i> , 352, 2271-84. <i>Not reported</i>

Source: Table 10, p52 of the submission.

6.6 The key features of the randomised trials are summarised in Table 4.

Table 4: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Population	Outcome(s)	Use in modelled evaluation
HZ/su vaccine vs. placebo						
ZOE-50	15,411	R, OB 3.2 years (mTVC)	Low	Healthy individuals aged ≥ 50 years (mean 62.3 years)	Primary: VE _{HZ} Secondary: VE _{PHN} , HZ complications, mortality, hospitalisations and pain, immunogenicity and reactogenicity, QoL outcomes	VE in terms of reduction in incidence of HZ and PHN in the overall population
ZOE-70	13,900	R, OB 3.7 years (mTVC)	Low	Healthy individuals aged ≥ 70 years (mean 75.6 years)	As above	As above
HZ-live vaccine vs. placebo						
SPS	38,546	R, OB 3.13 years (mITT)	Low	Healthy individuals aged ≥ 60 years (mean 69 years)	Primary: HZ burden of illness Secondary: VE _{HZ} , VE _{PHN} , HZ duration and severity	As above

HZ: herpes zoster; mITT: modified intent to treat; mTVC: modified total vaccinated cohort; OB: observer blind; PHN: post-herpetic neuralgia; QoL: quality of life; R: randomised; VE: vaccine efficacy
Source: Compiled during the evaluation.

6.7 The ZOE-50 and ZOE-70 trials were analysed on a modified total vaccinated cohort (mTVC), which excluded those who did not receive the second dose of the HZ/su vaccine (337 (4.4%) and 392 (5.6%) of individuals in the HZ/su treatment arms of ZOE-50 and ZOE-70, respectively) or those who had confirmed HZ within one month of receiving the second dose (4 individuals in the HZ/su arm and 14 individuals in the placebo arm of ZOE-50, and 4 individuals in the HZ/su arm and 11 individuals in the placebo arm of ZOE-70).

6.8 Overall, 95.4% of individuals enrolled in the HZ/su treatment arm and 96.1% of those in the placebo arm of the ZOE-50 trial were included in the mTVC. For the ZOE-70 trial, 94.1% of individuals enrolled in the HZ/su treatment arm and 95.2% of those in the placebo arm were included in the mTVC.

6.9 It was unclear why individuals with confirmed HZ within one month of receiving the second dose were excluded from the mTVC. Furthermore, it was unlikely that all individuals would receive both doses in clinical practice.

6.10 The ESC considered that the overall risk of bias was low in all trials.

Comparative effectiveness

6.11 Table 5 presents the results for vaccine efficacy, in terms of HZ cases, from the ZOE-50 and ZOE-70 trials (mTVC population).

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

Age strata	HZ/su vaccine				Placebo				VE _{HZ} *			p-value
	N	n	T (year)	n/T (per 1,000)	N	n	T (year)	n/T (per 1,000)	%	Lower 95% CI	Upper 95% CI	
ZOE-50												
50-59 years	3,492	3	11,161.3	0.3	3,525	87	11,134.7	7.8	96.57	89.62	99.31	<0.0001
60-69 years	2,141	2	7,007.9	0.3	2,166	75	6,952.7	10.8	97.36	90.14	99.69	<0.0001
≥70 years	1,711	1	5,127.9	0.2	1,724	48	5,083.0	9.0	97.93	87.91	99.95	<0.0001
≥60 years	3,852	3	12,135.7	0.2	3,890	123	12,035.7	10.2	97.58	92.77	99.51	<0.0001
≥50 years	7,344	6	23,297.0	0.3	7,415	210	23,170.5	9.1	97.16	93.72	98.97	<0.0001
ZOE-70												
70-79 years	5,114	17	19,346.5	0.9	5,189	169	19,247.5	8.8	90.02	83.54	94.32	<0.0001
≥80 years	1,427	6	5,058.5	1.2	1,433	54	4,920.3	11.0	89.08	74.65	96.16	<0.0001
≥70 years	6,541	23	24,405.1	0.9	6,622	223	24,167.8	9.2	89.79	84.29	93.66	<0.0001
Pooled ZOE-50 and ZOE-70												
70-79 years	6,468	19	24,410.9	0.8	6,554	216	24,262.8	8.9	91.27	86.04	94.85	<0.0001
≥80 years	1,782	6	6,314.6	1.0	1,792	68	6,151.9	11.1	91.37	80.22	96.94	<0.0001
≥70 years	8,250	25	30,725.5	0.8	8,346	284	30,414.7	9.3	91.30	86.88	94.46	<0.0001

CI: confidence interval; HZ: herpes zoster; HZ/su: recombinant varicella zoster vaccine; mTVC: modified total vaccine 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)

+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.

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

Source: Table 22 and 23 of the submission.

6.12 The HZ/su vaccine resulted in a statistically significant reduction in HZ cases across all age groups and the lower 95% confidence intervals (CI) for VE_{HZ} were all above 10%, which was the pre-defined minimum clinically important difference (MCID). VE_{HZ} was similar across age groups and the 95% CIs overlapped.

6.13 Table 6 presents vaccine efficacy for the TVC population, which included those individuals who had received one vaccination only.

Table 6: Results of vaccine efficacy against HZ cases (first or only episode) across the trials (TVC)

Age strata	HZ/su vaccine				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	
ZOE-50												
50-59 years	3,644	4	14,905.2	0.3	3,642	112	14,768.1	7.6	96.48	90.73	99.06	<0.0001
≥60 years	4,051	8	16,195.3	0.5	4,068	168	15,938.6	10.5	95.32	90.56	98.01	<0.0001
60-69 years	2,243	6	9,311.0	0.6	2,245	98	9,139.4	10.7	94.01	86.49	97.85	<0.0001
≥70 years	1,808	2	6,884.4	0.3	1,823	70	6,799.2	10.3	97.18	89.42	99.66	<0.0001
≥50 years	7,695	12	31,100.5	0.4	7,710	280	30,706.7	9.1	95.78	92.52	97.85	<0.0001
ZOE-70												
70-79 years	5,414	22	21,143.3	1.0	5,420	181	20,880.0	8.7	88.03	81.31	92.68	<0.0001
≥80 years	1,536	8	5,610.1	1.4	1,530	59	5,392.3	10.9	86.88	72.42	94.59	<0.0001
≥70 years	6,950	30	26,753.4	1.1	6,950	240	26,272.3	9.1	87.74	82.04	91.91	<0.0001

CI: confidence interval; HZ: herpes zoster; HZ/su: recombinant varicella zoster vaccine; 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; TVC: total vaccine cohort; VE: vaccine efficacy (Poisson method)

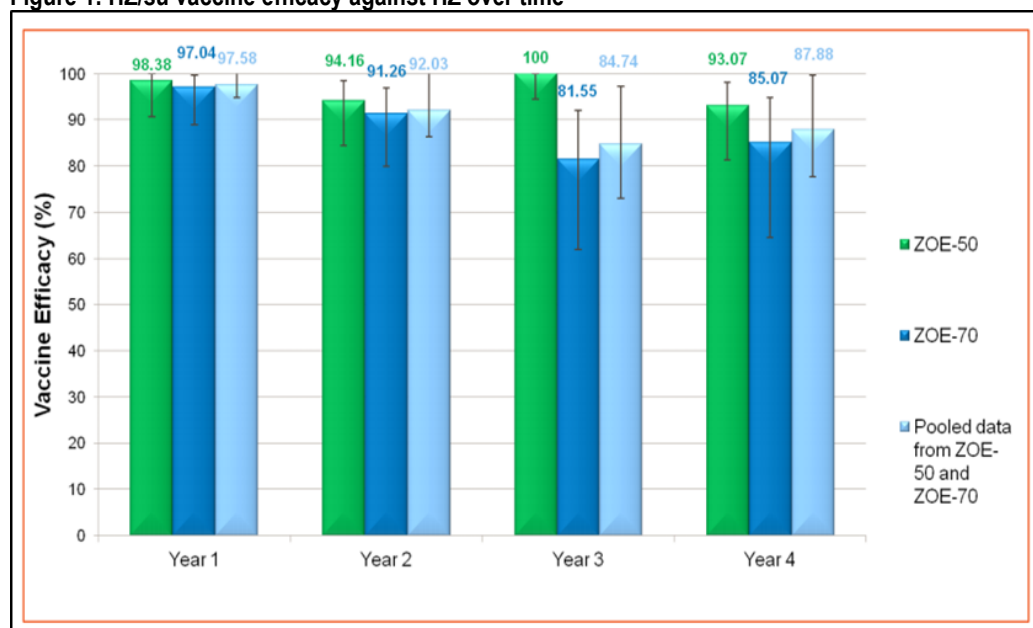
Source: Table 4, p6 and Table 6, p7 of the PSCR

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

6.14 VE_{HZ} in individuals aged 70+ years who received one dose (VE_{HZ} (pooled ZOE-50 and ZOE-70) = 69.51%, 95% CI: 24.9, 89.11) was lower than in individuals who received two doses (VE_{HZ} (pooled ZOE-50 and ZOE-70) = 91.30%, 95% CI: 86.88, 94.46). The ESC noted that the TVC population outcomes for VE_{HZ} were very similar to those for the mTVC populations in both trials and across all age groups, with only a small number of individuals, approximately 5%, not receiving a second dose.

6.15 Figure 1 presents VE_{HZ} over time.

Figure 1: HZ/su vaccine efficacy against HZ over time



HZ: herpes zoster; HZ/su: recombinant varicella zoster vaccine
Source: Figure 13, p76 of the submission.

6.16 Overall, VE_{HZ} waned slightly over four years (98.38% to 93.07% in the ZOE-50 trial, 97.04% to 85.07% in the ZOE-70 trial, and 97.58% to 87.88% in pooled data from the ZOE-50 and ZOE-70 trials). Mean follow-up was 3.2 and 3.7 years in the ZOE-50 and ZOE-70 trials respectively. This limited the ability to assess waning in the longer-term and the need for a booster dose, especially for individuals vaccinated at age 60. The PBAC noted that the duration of protection following a single dose of HZ/su was unknown.

6.17 The rate of waning in VE_{HZ} did not appear to differ substantially by age groups.

6.18 The PSCR provided results from a Phase IIIB, open-label study following participants for up to nine years after they had received two doses of the HZ/su vaccine. Schwartz et al, 2018 found that although both cell mediated immunity and humoral immune responses to the HZ/su vaccine decreased initially, both levelled off at around four years post-vaccination and remained stable, well-above baseline, for nine years in adults aged 60 years and over. In addition, the PSCR noted that the need for a booster

dose of the HZ/su vaccine has not been established and has not been formally recommended by immunisation committees such as the Advisory Committee on Immunization (ACIP, 2018) or ATAGI, 2018. The ESC noted that although Schwartz et al, 2018 was a small study (N = 70, mean age 72) which measured surrogate end points, given the high vaccine efficacy and slow rates of waning in the ZOE-50 trial over 3.2 years, waning of the HZ/su vaccine would likely take many years for the primary cohort of 60 year olds.

6.19 Table 7 presents the PHN results from the ZOE-50 and ZOE-70 trials.

Table 7: Results of vaccine efficacy against PHN cases (first or only episode) across the trials (mTVC)

Age strata	HZ/su vaccine				Placebo				VE _{PHN} [*]			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*	3,491	0	13,789.7	0	3,523	8	13,928.7	0.6	100	40.88	100.00	0.0081
60-69 years*	2,140	0	8,621.4	0	2,166	2	8,674.4	0.2	100	-442.83	100.00	0.5097
≥70 years*	1,709	0	6,323.4	0	1,724	8	6,340.6	1.3	100	41.40	100.00	0.0078
≥60 years*	3,849	0	14,944.8	0	3,890	10	15,015.0	0.7	100	55.25	100.00	0.0020
≥50 years**	7,340	0	28,734.6	0	7,413	18	28,943.7	0.6	100	77.11	100.00	<0.0001
ZOE-70												
70-79 years*	5,114	2	19,371.4	0.1	5,189	22	19,571.1	1.1	90.80	62.57	98.95	<0.0001
≥80 years*	1,427	2	5,065.5	0.4	1,433	6	5,030.3	1.2	65.75	-91.58	96.62	0.3072
≥70 years**	6,541	4	24,436.9	0.2	6,622	28	24,601.4	1.1	85.49	58.52	96.30	<0.0001
Pooled ZOE-50 and ZOE-70												
70-79 years*	6,468	2	24,438.8	0.1	6,554	29	24,660.4	1.2	93.04	72.47	99.19	<0.0001
≥80 years*	1,782	2	6,321.5	0.3	1,792	7	6,281.6	1.1	71.16	-51.51	97.08	0.1844
≥70 years**	8,250	4	30,760.3	0.1	8,346	36	30,942.0	1.2	88.78	68.70	97.10	<0.0001

CI: confidence interval; HZ/su: recombinant varicella zoster vaccine; mTVC: modified total vaccine cohort; N: number of subjects included in each group; n: number of subjects having at least one PHN case; PHN: post-herpetic neuralgia; 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; VE: vaccine efficacy (Poisson method)

+ 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.

* VE adjusted by region

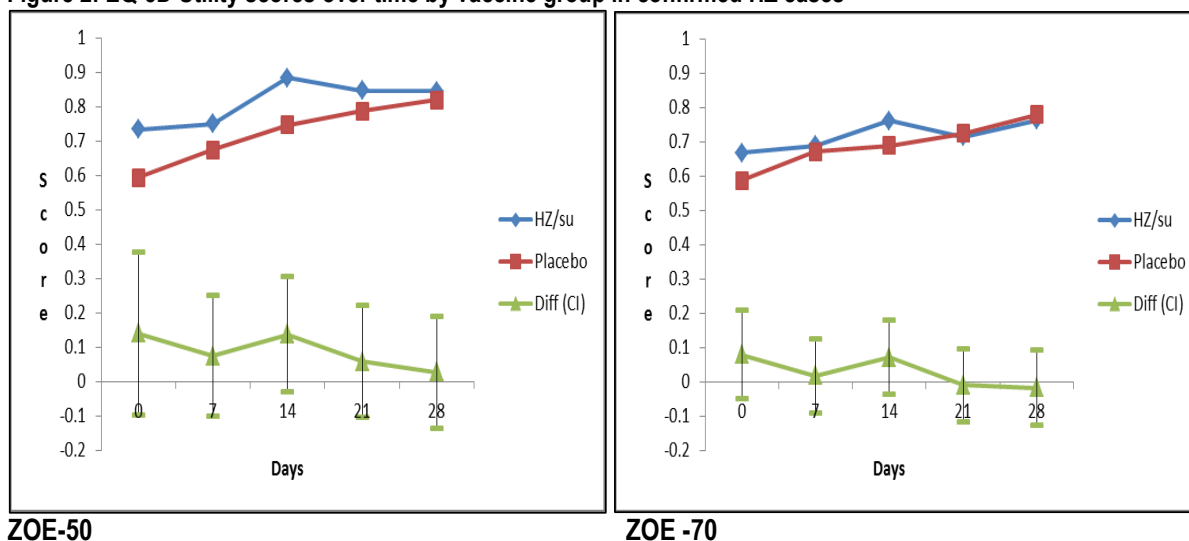
** VE adjusted by age strata and region

Source: Table 24 and 25 of the submission and added during the evaluation based on Table 34 of ZOSTER-006 CSR, and Table 25 of ZOSTER-022 CSR.

6.20 VE_{PHN} with the HZ/su vaccine was high for most age groups. In some groups, the difference was not statistically significant, although this may be due to a lack of powering and a low number of cases in the placebo group. Although the VE_{PHN} was numerically lower in older age groups, the 95% CIs across all age groups overlapped.

6.21 Figure 2 presents the EQ-5D utility values following a patient experiencing a HZ episode (UK, time trade-off tariff).

Figure 2: EQ-5D Utility scores over time by vaccine group in confirmed HZ cases



ZOE-50

ZOE-70

CI: confidence interval; Diff: difference; HZ: herpes zoster; HZ/su: recombinant varicella zoster vaccine

Source: Figure 16, p81 of the submission; J Gerontol A Biol Sci Med Sci 2018 Jun 27.

- 6.22 The results show that the estimated least squares mean utility value increased over time after HZ onset in all age strata, as individuals recovered from their HZ episode. Furthermore, the placebo group had a lower utility value at HZ onset. It might be expected that individuals who received the HZ/su vaccine to have a less severe case of HZ compared to individuals who received placebo; however, the difference between the two treatment groups was not statistically significant (P= [REDACTED] in ZOE-50 and P= [REDACTED] in ZOE-70).
- 6.23 To compare the HZ/su vaccine with the live-HZ vaccine which is currently available, the submission conducted an indirect comparison of pooled data from the ZOE-50 and ZOE-70 trials with data from the SPS trial, using placebo as a common comparator.
- 6.24 The submission stated that the Bucher method was used and a fixed effect analysis was conducted. The evaluation considered logs should have been taken to estimate the standard error as the confidence intervals were not symmetrical around the mean. Furthermore, some vaccine efficacy estimates applied in the analyses differed from those in the clinical study reports.
- 6.25 The trial designs and populations were reasonably similar, with the following exceptions: the ZOE-50/ZOE-70 pooled ≥ 70 years data set had a larger proportion of older participants aged ≥ 80 years (12.9%) compared with the SPS trial (approximately 7%); the SPS trial had an additional inclusion criteria of "history of varicella"; and the SPS trial was older, with results reported in 2005. The HZ event rate in the placebo arms of the pooled ZOE trials (9.3 per 1,000 years follow-up) and SPS (11.50 per 1,000 years) trials were similar. However, the PHN event rates in the placebo arms varied and was considerably higher in the SPS trial (2.13 per 1,000 years follow-up) compared to the pooled ZOE trials (1.2 1,000 years), suggesting there may be some important differences across the trials.

Table 10: Summary of key adverse events, pooled analysis of the ZOE-50 and ZOE-70 trials

Trial ID	HZ/su vaccine n/N (%)	Placebo n/N (%)	RR (95% CI)
Incidence of solicited local symptoms reported during the 7-day post-vaccination period (overall/subject)			
Pain			
All	3,810/4,884 (78.0%)	533/4,880 (10.9%)	NR
Grade 3	315/4,884 (6.4%)	17/4,880 (0.3%)	NR
Redness (mm)			
All	1,863/4,884 (38.1%)	64/4,880 (1.3%)	NR
> 100 mm	141/4,884 (2.9%)	0/4,880	NR
Swelling (mm)			
All	1,267/4,884 (25.9%)	48/4,880 (1.0%)	NR
> 100 mm	51/4,884 (1.0%)	0/4,880	NR
Incidence of solicited general symptoms (Grade 3) reported during the 7-day post-vaccination period (overall/subject)			
Fatigue	257/4,876 (5.3%)	50/4,881 (1.0%)	NR
Gastrointestinal symptoms	66/4,876 (1.4%)	27/4,881 (0.6%)	NR
Headache	162/4,876 (3.3%)	34/4,881 (0.7%)	NR
Myalgia	248/4,876 (5.1%)	33/4,881 (0.7%)	NR
Shivering	198/4,876 (4.4%)	13/4,881 (0.3%)	NR
Temperature > 39.0 degrees	14/4,876 (0.3%)	8/4,881 (0.2%)	NR
Other adverse events			
SAEs, at least one symptom	1,880/14,645 (12.8%)	1,945/14,660 (13.3%)	0.97 (0.91, 1.03); Unadjusted p-value = 0.31578
SAEs related to vaccination	15 (0.1%)	15 (0.1%)	
Discontinuation due to a SAE or AE	116/NR (NR)	65/NR (NR)	NR
Discontinuation due to an AE	62/NR (0.4%)	17/NR (0.1%)	NR
Discontinuation due to a SAE	54/NR (0.4%)	48/NR (0.3%)	NR

AE: adverse event; CI: confidence interval; HZ/su: recombinant varicella zoster vaccine; n: number of participants reporting data; N: total participants in group; NR: not reported; RR: relative risk; SAE: serious adverse event
Source: Table 33-36 p87 of the submission and GSK summary of safety 2017, p77

- 6.29 The ATAGI noted that rates of reactogenicity with the HZ/su vaccine were noticeably higher in the ZOE-50 and ZOE-70 trials compared to placebo. This was evident in the pooled results, which suggested higher rates of pain, redness and swelling. The incidence of Grade 3 adverse events was numerically higher for most events in the pooled HZ/su arm.
- 6.30 The ATAGI and ESC noted that although there were no major safety concerns identified, continuing safety monitoring would be of particular importance for the HZ/su vaccine given the novel adjuvant system used in the vaccine.
- 6.31 No formal indirect comparison of safety outcomes between the HZ/su vaccine and the live-HZ vaccine, using the ZOE-50, ZOE-70 and SPS trials was conducted by the submission.

6.32 A naïve indirect comparison demonstrated that individuals experienced higher rates of pain with the HZ/su vaccine (█████%) compared to the live-HZ vaccine (34.5%). Rates of erythema (redness) and swelling were similar. Individuals reported higher rates of serious adverse events with the HZ/su vaccine in the ZOE trials (█████%) compared to the live-HZ vaccine in the SPS trial (1.4%).

Benefits/harms

6.33 A summary of the comparative benefits and harms for the HZ/su vaccine versus no vaccine (placebo) is presented in Table 11.

Table 11: Summary of comparative benefits and harms for the HZ/su vaccine and no vaccine

Trial	N	VE, % (95% CI)	Event rate/year/1,000 individuals vaccinated*		Increment (per year)**	
			HZ/su	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	
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						
	HZ/su, n/N	PBO, n/N	RR (95% CI)	Event rate/1,000 individuals vaccinated*		RD**
				HZ/su	PBO	
Pain, Grade 3						
Pooled ZOE-50 and ZOE-70	315/4,884	17/4,880	NR	64	3	61
Redness > 100 mm						
Pooled ZOE-50 and ZOE-70	141/4,884	0/4,880	NR	29	0	29
Swelling > 100 mm						
Pooled ZOE-50 and ZOE-70	51/4,884	0/4,880	NR	10	0	10
Serious adverse events, at least one symptom						
Pooled ZOE-50 and ZOE-70	1,880/14,645	1945/14,660	0.97 (0.91-1.03)	128	133	-5

CI: confidence interval; HZ: herpes zoster; HZ/su: recombinant varicella zoster vaccine; 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; SAE: serious adverse event; VE: vaccine efficacy.

^persons aged ≥70 YOA

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

** Calculated during the evaluation

Source: Table 22 and 23 p73-74, Table 24 and 25 p74-75, and Table 33-36 p87 of the submission.

6.34 A summary of the comparative benefits and harms for HZ/su versus the live-HZ vaccine is presented in Table 12.

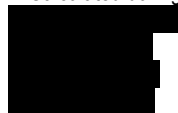
Table 12: Summary of comparative benefits and harms for the HZ/su vaccine and the live-HZ vaccine

	HZ/su, n/N	PBO, n/N	Live-HZ, n/N	VE (95% CI)	Event rate/year/1,000 individuals vaccinated*			Increment (per year)**
					HZ/su	PBO	Live-HZ	
Benefits								
Reduction in HZ cases: indirect comparison								
Pooled ZOE-50 and ZOE-70 (≥ 70 years)	25/8,250	284/8,346	-	0.91 (0.87, 0.94)	0.8	9.3	-	-8.5 (-10.5 if PBO = 11.5) ¹
SPS (≥ 70 years)	-	308/8,891	193/8,884	0.38 (0.25, 0.48)	-	11.5	7.2	-4.3 (-3.5 if PBO = 9.3) ²
Indirect comparison: Pooled ZOE-50 + ZOE-70 vs. SPS				██████████**	-			██████████
Reduction in PHN cases: indirect comparison								
Pooled ZOE-50 and ZOE-70 (≥ 70 years)	4/8,250	36/8,346	-	0.89 (0.69, 0.97)	0.1	1.2	-	-1.1 (-1.9 if PBO = 2.1) ³
SPS (≥ 70 years)	-	57/8,891	19/8,884	0.67 (0.43, 0.81)	-	2.1	0.7	-1.4 (-0.8 if PBO = 0.3) ⁴
Indirect comparison: Pooled ZOE-50 + ZOE-70 vs. SPS				██████████**	-			██████████
Harms								
	HZ/su or Live-HZ, n/N	PBO, n/N	RR (95% CI)	Event rate/1,000 individuals vaccinated*		RD**		
				HZ/su or Live-HZ	PBO			
Pain								
Pooled ZOE-50 + ZOE-70 (All)	3,810/4,884	533/4,880	NR	780	109	671		
SPS	1,147/3,345	278/3,271	NR	345	85	260		
Redness								
Pooled ZOE-50 + ZOE-70 (All)	1,863/4,884	64/4,880	NR	381	13	368		
SPS	1,188/3,345	227/3,271	NR	358	70	288		
Swelling								
Pooled ZOE-50 + ZOE-70 (All)	1,267/4,884	48/4,880	NR	259	10	249		
SPS	871/3,345	147/3,271	NR	262	45	217		
Serious adverse events, at least one symptom								
Pooled ZOE-50 + ZOE-70 (All)	1,880/14,645	1,945/14,660	0.97 (0.91, 1.03)	128	133	-5		
SPS	255/18,671	254/18,717	1.01 (0.85, 1.20)	14	14	0		

CI: confidence interval; HZ: herpes zoster; HZ/su: recombinant varicella zoster vaccine; 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; SAE: serious adverse event; VE: vaccine efficacy.

* Mean duration of follow-up: ZOE-50 = 3.2 years; ZOE-70 = 3.7 years; SPS = 3.13

** Calculated during the evaluation



Source: Table 29 p92 and Table 40 p93 of the submission, and Oxman (2005) and Zostavax PI.

6.35 On the basis of direct evidence presented by the submission, for every 1,000 individuals aged over 50 years vaccinated with the HZ/su vaccine in comparison to placebo and over a mean duration of follow-up of 3.2 to 3.7 years:

- Approximately 8 to 9 fewer individuals per year would have HZ.
 - Approximately 1 fewer individuals per year would have PHN.
 - Approximately 61 additional individuals would experience Grade 3 pain.
 - Approximately 29 additional individuals would experience redness >100 mm.
 - Approximately 10 additional individuals would experience swelling >100 mm.
- 6.36 On the basis of the naïve indirect comparison evidence presented by the submission, for every 1,000 individuals aged over 70 years vaccinated with the HZ/su vaccine in comparison to the live-HZ vaccine and over a mean duration of follow-up of 3.2 to 3.7 years:
- Approximately [REDACTED] fewer individuals per year would have HZ.
 - Approximately [REDACTED] fewer individuals per year would have PHN.
 - Approximately [REDACTED] additional individuals would experience any pain.
 - Approximately [REDACTED] additional individuals would experience any redness.
 - Approximately [REDACTED] additional individuals would experience any swelling.

Clinical claim

- 6.37 The submission described two doses of the HZ/su vaccine as having:
- Superior efficacy and a similar safety profile, despite being more reactogenic, compared with the live-HZ vaccine, the current funded standard of care for individuals aged 70 to 79 years; and.
 - Superior efficacy and slightly inferior safety when compared with no vaccine (placebo) for individuals aged 60 to 69 years and 80 years and over.
- 6.38 In terms of efficacy, the ESC considered that the HZ/su vaccine was superior to placebo and the live-HZ vaccine. However, the ESC considered that the magnitude of benefit in both comparisons should be considered with caution as:
- The trials excluded individuals who had previously experienced HZ, had previously received a varicella/HZ vaccine, or were immunocompromised or immunosuppressed. While some immunogenicity data were available, ATAGI advised that there was no established immunocorrelate of protection for HZ. Consequently, the incremental benefit of vaccinating these individuals was unknown. It is likely that the clinical efficacy is less than in immunocompetent individuals (ATAGI pre-submission advice, p20), and individuals with recent HZ episode history (≤ 4 years) (Gordeaux et al, 2017). No evidence was available on the incremental benefit of vaccinating individuals with the HZ/su vaccine who had recently received (within five years) the live-HZ vaccine.
 - Overall, VE_{HZ} waned by approximately 10% over the four years of ZOE trial follow-up. The short follow-up limited the ability to assess waning in the longer-term and the need for a booster dose, particularly for individuals aged 60 years. However, the ESC considered that given the high vaccine efficacy and slow rates of waning in the ZOE-50 trial over 3.2 years, waning of the HZ/su vaccine would likely take

many years for the primary cohort of 60 year olds.

- In the indirect comparison between the HZ/su and live-HZ vaccines, the PHN event rates were considerably higher in the SPS trial (2.13 per 1,000) compared to the ZOE-50 (0.6 per 1,000) and ZOE-70 trials (1.1 per 1,000).
- 6.39 The ESC considered the safety conclusions regarding the HZ/su vaccine compared to no vaccine (placebo) and to the live-HZ vaccine presented by the submission were reasonable.
- 6.40 The PBAC considered that the claim of superior comparative effectiveness and similar safety to the live HZ vaccine was reasonable.
- 6.41 The PBAC considered that the claim of superior comparative effectiveness and 'slightly' inferior safety to no vaccine was reasonable, with the PBAC noting the increased frequency of injection site reactions compared to placebo.

Economic analysis

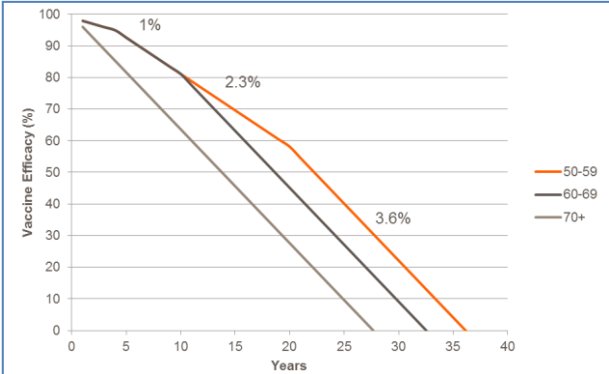
- 6.42 The submission presented a stepped, modelled economic evaluation based on direct randomised trials. The type of economic evaluation presented was a cost-utility analysis.
- 6.43 Although the ESC considered that the HZ/su vaccine would provide direct benefits to the treated individual, it was concerned about the high opportunity costs. The ESC recalled that the threshold of incremental quality-adjusted life years (QALYs) gained previously accepted by the PBAC for treatments with large opportunity costs, such as population preventative interventions including lipid-lowering, anti-hypertensive drugs and vaccines, was at the lower end of the ICER range. Therefore, the ESC considered that the acceptable ICER for the HZ/su vaccine should also be at the lower end of the range previously accepted for other population preventative interventions with large opportunity costs.
- 6.44 The submission presented three analyses across three age groups. It was noted that the ongoing NIP cohort would be for 60-year olds only, and there would be no separate ongoing 70-year old or 80-year old program. The analyses were:
- HZ/su vaccine, given as two doses two months apart, compared to no vaccination in Australian adults aged 60 years of age;
 - HZ/su vaccine, given as two doses two months apart, compared to the live-HZ vaccine, given as a single dose, in Australian adults aged 70 years of age; and
 - HZ/su vaccine, given as two doses two months apart, compared to no vaccination in Australian adults aged 80 years.
- 6.45 The PBAC noted a comparison of the proposed vaccination program (two doses of HZ/su vaccine at age 60 years) versus the current vaccination program (a single dose of the live-HZ vaccine at 70 years) was not presented in the submission.

Table 13: Summary of model structure and rationale

Component	Summary
Type of analysis	Cost-utility analysis
Outcomes	QALYs. The submission also presented disaggregated results for number of HZ cases, PHN cases, HZ-related complications and HZ-related deaths.
Time horizon	The multi-cohort model simulated the impact of HZ disease over the remaining life-time from the year of vaccination, with annual cycles. In comparison, the mean follow-up was 3.2 and 3.7 years in the ZOE-50 and ZOE-70 trials respectively. This introduced uncertainty regarding waning in the longer term and the need for a booster dose, especially for individuals aged 60 years.
Methods used to generate results	Markov model.
Health states	No HZ; HZ; Natural death; HZ related deaths; Recovered; and Recurrent HZ. PHN and non-PHN complications (ocular, neurological, cutaneous, and other non-pain complications) occurred within a HZ episode.
Cycle length	One year
Transition probabilities	Age specific all-cause mortality (ABS data). This was appropriate. Age specific annual incidence of HZ and PHN incidence as a proportion of HZ was source from MacIntyre et al. (2015), which was based on encounters recorded in the Bettering the Evaluation and Care of Health (BEACH) GP database between 2006-2013 (N = 6,302 GPs and 630,200 GP-patient encounters, resulting in 655 new cases of HZ managed at GP encounters and 93 new cases of PHN). The incidence of HZ and PHN were based on BEACH data rather than on the placebo arms of the ZOE trials as the submission concluded that the exclusion criteria of the trials meant the trial population was healthier than the general Australian population. The ESC considered this may have been reasonable as it increased the applicability to the Australian context, was consistent with ATAGI pre-submission advice and was consistent with the 2014 PBAC submission for the live-HZ vaccine ² . However, it was noted that the sensitivity analyses that used the lower HZ rate observed in the placebo arms of the ZOE trials had a large effect on the ICER, and also that BEACH data has become less reliable over time, with lower participation rates. The ESC considered the exclusion of immunocompromised patients from the ZOE trials may not sufficiently explain the large discrepancy in the incidence of HZ and PHN in the BEACH data compared to the ZOE trial data. The ESC considered a more reliable ICER may lie somewhere in between. The pre-PBAC Response reiterated that the BEACH data was the most valid source as it evaluated the impact of the vaccine on the Australian population. Incidence of recurrent HZ and PHN was assumed to be the same as HZ and PHN incidence based on MacIntyre et al (2015), supported by Yawn et al (2011) (N = 1,669). Although Yawn et al (2011) estimated a recurrence rate lower than the incidence of HZ estimated by MacIntyre et al (2015), the rate reported by Yawn et al (2011) was generally higher than the recurrence rate reported by other published studies. Thus, the recurrence rate applied in the model may have been overestimated. The ESC noted that the ICER was sensitive to this estimate and that the approach favoured the HZ/su vaccine. HZ-related fatality was sourced from Le and Rothberg (2015), and based on Centers for Disease Control and Prevention (CDC) WONDER mortality data from 1999 to 2012. The application of US data to the Australian context was uncertain. Probability of non-PHN complications (zoster ophthalmicus, neurological complications, cutaneous, other non-pain) was sourced from Yawn et al (2007), and based on a population-based US study (N = 1,669). This was reasonable, given that available Australian data was for hospitalised cases only. Trial-based VE_{HZ} : HZ/su vaccine (ZOE-50 and ZOE-70); live-HZ vaccine (SPS). The submission assumed that VE_{HZ} at Year 0 was based on the intercept from a linear model used to characterise waning over four years. The approach likely overestimated efficacy in those aged 80 years and

² PBAC (March 2014) Public summary document: Zoster virus vaccine live, 0.65 mL injection, prefilled syringe, Zostavax

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Component	Summary																													
	<p>over. The ICER was sensitive to waning, especially the rate applied when the individual reaches 70 years, which remained uniform (3.6%) from this point. The extent to which the results were sensitive to the initial estimates of vaccine efficacy was unknown.</p> <p>It was assumed that $VE_{PHN} = VE_{HZ}$ for all time periods. The evaluator considered that this was not justified and was not appropriate, especially for the older age groups.</p> <p>It was assumed that VE_{HZ} (and thus VE_{PHN}) following one dose of the HZ/su vaccine waned at the same rate as the live-HZ vaccine. This was uncertain.</p> <p>VE_{HZ} of the HZ/su vaccine at Year 0</p> <table border="1" data-bbox="352 640 1382 981"> <thead> <tr> <th rowspan="2">Age strata</th> <th colspan="2">VE_{HZ}</th> <th colspan="2">VE_{PHN}</th> </tr> <tr> <th>Trial</th> <th>Model at Year 0</th> <th>Trial</th> <th>Model at Year 0</th> </tr> </thead> <tbody> <tr> <td>50-59</td> <td>Over 3.2 years: 96.57 (ZOE-50) In Year 1: 96.76 (ZOE-50)</td> <td>98.4</td> <td>Over 3.1 years: 100 In Year 1: NR</td> <td>98.4</td> </tr> <tr> <td>60-69</td> <td>Over 3.2 years: 97.36 (ZOE-50) In Year 1: 100.00 (ZOE-50)</td> <td>98.4</td> <td>Over 3.1 years: 100 In Year 1: NR</td> <td>98.4</td> </tr> <tr> <td>70-79</td> <td>Over 3.2-3.7 years: 91.27 (ZOE-50/ZOE-70) In Year 1: 98.23 (ZOE-50/ZOE-70)</td> <td>97.8</td> <td>Over 3.1-3.7 years: 93.04 In Year 1: NR</td> <td>97.8</td> </tr> <tr> <td>80+</td> <td>Over 3.2-3.7 years: 91.37 (ZOE-50/ZOE-70) In Year 1: 96.16 (ZOE-50/ZOE-70)</td> <td>97.8</td> <td>Over 3.1-3.7 years: 71.16 In Year 1: NR</td> <td>97.8</td> </tr> </tbody> </table> <p>Source: compiled during evaluation</p> <p>Waning of VE_{HZ} for 2 doses of the HZ/su vaccine over time</p>  <p>The ESC noted that the long-term rates of waning applied in the model were optimistic when compared to the short-term rates seen in the ZOE-50 trial (approximately 5.3% over 4 years, or 1.3% per year) and the ZOE-70 trial (approximately 12% over 4 years, or 3% per year). The pre-PBAC Response considered that the rates calculated by ESC were similar to those used in the model (50-69 years: 1% annual waning rate for the first four years post-vaccination, followed by 2.3% annual waning rate until 70; and ≥ 70 years: 3.6% annual waning rate) which were also calculated using the four-year time points. The PBAC considered that the application of these rates in the long-term introduced uncertainty.</p> <p>Compliance was trial based (ZOE-50 and ZOE-70). It was assumed that people who experienced solicited or unsolicited local or general Grade 3 reactions in the 7 days following the 1st dose in the ZOE-50 and ZOE-70 trials did not receive a second dose. This was consistent with ATAGI pre-submission advice. An average of 1.9 doses was assumed in the model.</p>	Age strata	VE_{HZ}		VE_{PHN}		Trial	Model at Year 0	Trial	Model at Year 0	50-59	Over 3.2 years: 96.57 (ZOE-50) In Year 1: 96.76 (ZOE-50)	98.4	Over 3.1 years: 100 In Year 1: NR	98.4	60-69	Over 3.2 years: 97.36 (ZOE-50) In Year 1: 100.00 (ZOE-50)	98.4	Over 3.1 years: 100 In Year 1: NR	98.4	70-79	Over 3.2-3.7 years: 91.27 (ZOE-50/ZOE-70) In Year 1: 98.23 (ZOE-50/ZOE-70)	97.8	Over 3.1-3.7 years: 93.04 In Year 1: NR	97.8	80+	Over 3.2-3.7 years: 91.37 (ZOE-50/ZOE-70) In Year 1: 96.16 (ZOE-50/ZOE-70)	97.8	Over 3.1-3.7 years: 71.16 In Year 1: NR	97.8
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70-79	Over 3.2-3.7 years: 91.27 (ZOE-50/ZOE-70) In Year 1: 98.23 (ZOE-50/ZOE-70)	97.8	Over 3.1-3.7 years: 93.04 In Year 1: NR	97.8																										
80+	Over 3.2-3.7 years: 91.37 (ZOE-50/ZOE-70) In Year 1: 96.16 (ZOE-50/ZOE-70)	97.8	Over 3.1-3.7 years: 71.16 In Year 1: NR	97.8																										
Utilities	<p>No condition – based on age specific baseline utilities from Clemens et al (2014), an Australian study which utilised a EQ-5D-3L data set in the Queensland population. This was an appropriate source; however, the age groups used in the submission varied compared to the age groups used in Clemens et al (2014). The baseline utility values presented in the submission may have been overestimated; however, the impact on the ICER was likely to be modest.</p>																													

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Component	Summary
	<p>The submission estimated utilities with HZ using published data, rather than using the utilities estimated in the ZOE-50 and ZOE-70 trials.</p> <p>QALY loss per HZ case without PHN – Gater et al (2014) and MacIntyre et al (2015). This was reasonable</p> <p>QALY loss per HZ case with PHN –Serpell et al (2014) and Moore et al (2010). This was reasonable.</p> <p>QALY loss per local/general AE reactions – assumed. This was uncertain.</p> <p>QALY loss per hospitalisation – Le and Rothberg (2015). This was unable to be verified.</p>

ABS: Australian Bureau of Statistics; ATAGI: Australian Technical Advisory Group on Immunisation; GP: general practitioner; HZ: herpes zoster; ICER: incremental cost-effectiveness ratio; NR: not reported; PBAC: Pharmaceutical Benefits Advisory Committee; PHN: post-herpetic neuralgia; QALY: quality adjusted life year; VE: vaccine efficacy.

Source: Table 44 p102 of the submission.

6.46 The key drivers of the model and results are provided in the tables below.

Table 14: Key drivers of the model

Description	Method/Value	Impact
Time horizon/waning	Lifetime horizon, with rate of waning of vaccine efficacy applied dependent on age, compared to 3.1 to 3.7 years in ZOE-50 and ZOE-70 trials.	High, favours the HZ/su vaccine
Incidence of HZ and PHN in placebo arm	Based on MacIntyre (2015)/BEACH data rather than incidence reported in the placebo arms of the trials.	High, favours the HZ/su vaccine
Revaccination of those who had previously received the live-HZ vaccine	Not addressed in the model. It was assumed that the live-HZ vaccine was replaced and that individuals had not been previously vaccinated.	High, favours the HZ/su vaccine
Recurrence	Incidence of recurrent HZ and PHN was assumed to be the same as HZ and PHN incidence reported in MacIntyre (2015). The ESC noted that other data sources reported lower incidences for recurrence.	Moderate, favours the HZ/su vaccine
QALY loss per HZ case ± PHN	Gater et al (2014) and Serpell et al (2014)	Moderate, unknown direction
Efficacy	Trial-based VE_{HZ} : HZ/su vaccine (ZOE-50 and ZOE-70); live-HZ vaccine (SPS). Efficacy at Year 0 was based on the intercept after fitting a linear function to trial data. It was assumed that $VE_{PHN} = VE_{HZ}$.	Unknown impact

HZ: herpes zoster; HZ/su: recombinant varicella zoster vaccine; PHN: post-herpetic neuralgia; QALY: quality adjusted life year; VE: vaccine efficacy.

Source: Compiled during the evaluation.

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Table 15: Results of the economic evaluation (theoretical cohort of one million)

Age group and component	HZ/su vaccine	No vaccine or live-HZ vaccine	Increment
60 year olds			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
HZ cases	173,764 (of which 23,950 (14%) were recurrent)	382,719 (of which 71,450 (19%) were recurrent)	-208,955
PHN cases	41,133	79,957	-38,824
QALYs	11,668,204	11,660,781	7,423
Incremental cost/extra QALY gained			\$ [REDACTED]
70 year olds			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
HZ cases	120,073 (of which 13,809 (12%) were recurrent)	239,529 (of which 32,580 (14%) were recurrent)	-119,456
PHN cases	29,902	46,009	-16,107
QALYs	8,935,909	8,931,883	4,026
Incremental cost/extra QALY gained			\$ [REDACTED]
80 year olds			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
HZ cases	47,597 (of which 3,834 (8%) were recurrent)	164,331 (of which 16,231 (10%) were recurrent)	-116,734
PHN cases	12,375	42,726	-30,351
QALYs	5,652,413	5,645,029	7,384
Incremental cost/extra QALY gained			\$ [REDACTED]

HZ: herpes zoster; HZ/su: recombinant varicella zoster vaccine; PHN: post-herpetic neuralgia; QALY: quality adjusted life year
Source: Table 82 p159, table 86 p159 and table 90 p169 of the submission.

The redacted table shows ICERs in the range of \$15,000/QALY - \$45,000/QALY.

6.47 The results of the economic evaluation should be considered with caution as:

- The time horizon of the model was the individuals' lifetime (up to 114 years old). In comparison, the mean follow-up in the ZOE trials was 3.2 and 3.7 years. The long time horizon in the model introduced uncertainty surrounding waning in the longer term. The submission applied different rates that were dependent on the individual's age in the model, and after 28 to 33 years, vaccine efficacy was nil. The ICER was sensitive to waning, especially the rate applied when the individual reaches 70 years (3.6% per year) and which remained uniform from this point. The PSCR conducted a sensitivity analysis in the 60 year old cohort based on the range obtained when the rate of waning once an individual reached 70 years was bootstrapped (base case = 3.6%; range: 1.4%, 6.6%). Applying this range varied the ICER from \$15,000/QALY - \$45,000/QALY to \$15,000/QALY - \$45,000/QALY per QALY gained, a difference of ± 25%. The PBAC noted the ICER was sensitive to the assumed rate of waning and considered the rates applied were uncertain. The PBAC considered that the application of a rate of waning for patients once they reached 70 years (3.6%), which was calculated using less than four years follow-up data from patients vaccinated at 70 years of age and over, created uncertainty. The PBAC were concerned that for patients vaccinated at 60 years of age, the rate of waning once they reach 70 years might differ from the rate of waning for those who were vaccinated at 70 years. The PBAC considered that the uncertainty of

how waning would progress over the longer-term was not adequately addressed by the application of the bootstrapped range.

- The ESC noted that the long-term rates of waning applied in the model were optimistic when compared to the short-term rates seen in the ZOE-50 trial (approximately 5.3% over 4 years, or 1.3% per year) and the ZOE-70 trial (approximately 12% over 4 years, or 3% per year) and resulted in considerable uncertainty. The ESC suggested that the use of observed vaccine efficacy by age group and year up to Year 4, with assumed rates applied from Year 5 could be informative. The pre-PBAC Response considered that the rates calculated by ESC were similar to those used in the model (60-69 years: 1% annual waning rate for the first four years post-vaccination, followed by a rate of 2.3% per year until 70 years; ≥ 70 years: 3.6% annual waning rate). As discussed in the dot-point above, the PBAC considered that the application of the short-term rate of waning for those aged 70 years and over in the longer-term was optimistic and did not capture the uncertainties surrounding how waning might progress.
- The submission assumed that the cost of the live-HZ vaccine would be replaced; however, the proposed NIP listing for the HZ/su vaccine allows for re-vaccination of individuals who have received the live-HZ vaccine. The submission did not estimate the cost-effectiveness of re-vaccinating 70 year olds with the HZ/su vaccine who had recently received the live-HZ vaccine. The PSCR argued that re-vaccination with the HZ/su vaccine immediately after individuals received the live-HZ vaccine (Zostavax) would be unrealistic for a population immunisation program, and considered a more appropriate analysis would be based on the waning estimates of the live-HZ vaccine. The PSCR suggested a re-vaccination program five years after the initial vaccination, which resulted in an ICER of \$15,000/QALY - \$45,000/QALY for those aged 70 years. This ICER was unable to be verified. Given the improved effectiveness of the HZ/su vaccine, the PBAC considered that re-vaccination was likely.
- The submission assumed that VE_{PHN} was the same as VE_{HZ} . The impact of this on the ICER was unknown. The PBAC considered, as the VE_{PHN} results from the ZOE trials were uncertain due to a lack of powering and a small number of PHN events.
- The baseline incidences of HZ and PHN were based on BEACH data, rather than the placebo arms of the ZOE trials (see Table 16). Although the ESC agreed that it was reasonable to use BEACH data, the effect on the ICER was significant – using trial rates increased the ICER in the 60 year old cohort from \$15,000/QALY - \$45,000/QALY to \$75,000/QALY - \$105,000/QALY. The pre-PBAC Response reiterated that the BEACH data was the most valid source as it evaluated the impact of the vaccine on the Australian population. The PBAC considered the use of baseline incidences of HZ and PHN in the model that were substantially higher than those in the trial was not adequately justified.

Table 16: Incidence of HZ and PHN comparison from economic model versus clinical trial data

	Incidence of HZ		Incidence of PHN given HZ	
MacIntyre et al 2015, BEACH data (Economic model)	60–64	1.3600%	60–64	15%
	65–69	1.3600%	65–69	15%
	70–79	1.5300%	70–79	22%
	≥80	1.9000%	≥80	26%
ZOE trials (Clinical trial data)	60–64	1.080%	60–64	2.667%
	65–69	1.080%	65–69	2.667%
	70–79	0.890%	70–79	13.426%
	≥80	1.110%	≥80	10.294%

HZ: Herpes zoster; PHN: post-herpetic neuralgia

Source: Section 3_Shingrix CE Model_JULY 2018.xlsx

- The recurrence rates for HZ and PHN with no vaccine applied in the model were assumed to be equal to the initial incidence rate HZ with no vaccine (1.36% to 1.90%, depending on the age of the individual). Published studies suggest that the recurrence rate of HZ may be 0.683%; hence, the rate in the model may have been overestimated, which favoured the intervention. The PSCR acknowledged that there was variation in the recurrence rate of HZ in the literature.
- The modelled number of HZ (and PHN) cases avoided was substantially higher than the number avoided in the trial. Based on the trial results, vaccinating 1,000,000 individuals aged over 50 years would result in approximately 32,000 to 36,000 cases of HZ avoided over 4 years (see paragraph 6.33). This was consistent with Step 1 of the economic model (trial based analysis), which estimated 34,160 HZ cases avoided over the first four years if individuals were vaccinated at age 60 years. However, the base case model predicts 209,000 HZ cases avoided over the time horizon of the model. The magnitude of this difference highlights the uncertainty with the model results.

6.48 In the submission, the cost of each dose of the HZ/su was [REDACTED] (each dose of HZ/su cost \$ [REDACTED] (total cost for two doses = \$ [REDACTED]). The cost-effectiveness of vaccinating individuals aged 70 years was sensitive to the cost of the live-HZ vaccine used (the actual NIP cost of the live-HZ vaccine was lower than the commercial cost). All ICERs were sensitive to variations in the costs of the HZ/su and live-HZ vaccines.

6.49 Table 17 presents the key sensitivity analyses.

Table 17: Summary of key scenario and sensitivity analysis results

Analysis	Incremental costs	QALYs gained	Discounted ICER (\$/QALY gained)
Base case 60 YOA	\$ [REDACTED]	7,423	[REDACTED]
HZ recurrence rate with no vaccine = 0.683% of individuals (base case = 1.36 % to 1.90%)	\$ [REDACTED]	6,689	[REDACTED]
HZ and PHN incidence with no vaccine reported in ZOE placebo arms (base case = MacIntyre 2015)	\$ [REDACTED]	3,246	[REDACTED]
QALY loss per unvaccinated HZ case without PHN = 0.01 for individuals ≤ 69 years and 0.012 for > 70 years (base case = 0.0231 to 0.0247)	\$ [REDACTED]	5,666	[REDACTED]
QALY loss per unvaccinated HZ case with PHN = 0.106 for individuals ≤ 69 years and 0.156 for > 70 years (base case = 0.181 to 0.2268)	\$ [REDACTED]	5,728	[REDACTED]
Annual waning of HZ/su vaccine (two dose) HZ efficacy for 70 YOA and older = 6.6% (base case = 3.6%)	\$ [REDACTED]	6,379	[REDACTED]
Base case 70 YOA (versus live HZ vaccine)	\$ [REDACTED]	4,026	[REDACTED]
HZ recurrence rate with no vaccine = 0.683% of individuals (base case = 1.53 % to 1.90%)	\$ [REDACTED]	3,379	[REDACTED]
HZ and PHN incidence with no vaccine reported in ZOE placebo arms (base case = MacIntyre 2015)	\$ [REDACTED]	1,727	[REDACTED]
Removing the cost of the live-HZ vaccine as a cost-offset (i.e. live-HZ vaccine cost = \$0)	\$ [REDACTED]	4,026	[REDACTED]
Annual waning of HZ/su vaccine (two dose) HZ efficacy for 70 YOA and older = 6.6% (base case = 3.6%)	\$ [REDACTED]	5,724	[REDACTED]
Base case 80 YOA	\$ [REDACTED]	7,384	[REDACTED]
HZ recurrence rate with no vaccine = 0.683% of individuals (base case = 1.90%)	\$ [REDACTED]	7,029	[REDACTED]
HZ and PHN incidence with no vaccine reported in ZOE placebo arms (base case = MacIntyre 2015)	\$ [REDACTED]	2,506	[REDACTED]
QALY loss per unvaccinated HZ case with PHN for 80+ YOA = 0.156 (base case = 0.2268)	\$ [REDACTED]	5,251	[REDACTED]
Annual waning of HZ/su vaccine (two dose) HZ efficacy for 70 YOA and older = 6.6% (base case = 3.6%)	\$ [REDACTED]	6,283	[REDACTED]

HZ: herpes zoster; HZ/su: recombinant varicella zoster vaccine; ICER: incremental cost-effectiveness ratio; PHN: post-herpetic neuralgia; QALY: quality adjusted life year; YOA: years of age.

Source: Table 95, p174 of the submission and calculated during the evaluation in brackets.

The redacted table shows ICERs in the range of \$15,000/QALY - \$45,000/QALY to \$105,000/QALY - \$200,000/QALY.

Drug cost/course

6.50 The submission estimated that the expected cost of the HZ/su vaccine was \$ [REDACTED] per individual. This was based on two doses and a cost of \$ [REDACTED] per dose, [REDACTED]

Estimated NIP usage & financial implications

6.51 This submission was not considered by DUSC.

6.52 The submission used an epidemiological approach to estimate the financial impact of listing the HZ/su vaccine to the NIP and Australian Government health budget. The key

data sources included the ABS, the Chemist Warehouse (for the price of the live-HZ vaccine, \$ [REDACTED]) and the ATAGI pre-submission advice.

6.53 The ESC noted that the ongoing NIP cohort was 60-year olds only and that there was no separate ongoing 70-year old or 80-year old program. The utilisation in the five-year catch-up program cohorts was assumed to be 30% in Year 1, 20% in Year 2 and 10% in Years 3 to 5.

6.54 As presented in the table below, the overall cost to the NIP for both programs was estimated, by the submission, to be more than \$100 million over the first six years of listing. The Pre-PBAC Response stated that the potential cost was based on the assumptions that 30% of individuals turning 60 years of age each year and 80% of patients aged over 60 years would be vaccinated over the six years.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of individuals vaccinated						
60 year old program (31%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
70 year old program (49%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
80 year old program (59%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
60-69 year catch-up	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
70-79 year catch-up	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
80+ year catch-up	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of doses dispensed ^a						
60 year old program	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
70 year old program	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
80 year old program	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
60-69 year catch-up	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
70-79 year catch-up	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
80+ year catch-up	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated financial implications of the HZ/su vaccine to NIP						
60 year old program	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
70 year old program	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
80 year old program	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
60-69 year catch-up	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
70-79 year catch-up	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
80+ year catch-up	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated cost-savings from replacing the live-HZ vaccine to the NIP						
70 year old program	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
70-79 year catch-up	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net financial implications						
Net cost to NIP	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost to PBS/RPBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost to MBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

HZ: herpes zoster; HZ/su: recombinant varicella zoster vaccine; MBS: Medical Benefits Scheme; NIP: National Immunisation Program; PBS: Pharmaceutical Benefits Schedule; RPBS: Repatriation Pharmaceutical Benefits Schedule

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^a Assuming 1.9 doses per person, as estimated by the submission.

Italicised values calculated or corrected during evaluation.

Source: Table 102-7 p193-6.

The redacted table shows that at Year 5, the estimated number of doses dispensed for each age group ranged from 100,000 – 200,000 per year to over 200,000 per year, and the net financial implication to the NIP would be more than \$100 million per year.

- 6.55 The submission excluded individuals aged 70-79 years who were recently vaccinated (i.e. within five years) with the live-HZ vaccine from the calculations. The PSCR stated that it was unrealistic to assume that individuals would be re-vaccinated immediately.
- 6.56 The ESC considered that the cost to the NIP in Year 6 may have been overestimated as it included individuals in the '70 year old program' and '80 year old program', which was inconsistent with the proposed five-year catch-up program. The ESC considered that the corrected estimated net cost to the NIP in Year 6 (see Table 19 below) would be closest to the steady state cost of the listing (i.e. approximately \$30 - \$60 million per year). The ESC also noted the costs of the '60 year old program', '70 year old program' and '80 year old program' were inconsistent with the proposed NIP listing for 60 year old patients only, as the catch up programs across all age groups were accounted for separately. Removing the costs of the '70 year old program' and '80 year old program', adjusting the 60-69 year old catch-up to not double count uptake in the '60 year olds program' resulted in an overall net cost to the NIP, which included the savings from the live-HZ vaccine, of more than \$100 million over the first six years (see table below).

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Table 19: Overall cost to the NIP for the HZ/su vaccine program and catch-up program (excluding the MBS fee) with HZ/su vaccine and live-HZ vaccine = \$185 per dose

Item	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Estimated extent of use							
Number of individuals vaccinated							
60 year old program	██████	██████	██████	██████	██████	██████	██████
61-69 year catch-up	██████	██████	██████	██████	██████		██████
70-79 year catch-up	██████	██████	██████	██████	██████		██████
80+ year catch-up	██████	██████	██████	██████	██████		██████
Number of scripts dispensed ^a							
60 year old program	██████	██████	██████	██████	██████	██████	██████
61-69 year catch-up	██████	██████	██████	██████	██████		██████
70-79 year catch-up	██████	██████	██████	██████	██████		██████
80+ year catch-up	██████	██████	██████	██████	██████		██████
Total cost of HZ/su vaccine to NIP for 60+ years old population group							
Base case	██████	██████	██████	██████	██████	██████	██████
Catch-up	██████	██████	██████	██████	██████	██████	██████
Total	██████	██████	██████	██████	██████	██████	██████
Total cost of HZ/su vaccine to NIP for 70+ years old population group							
Catch-up	██████	██████	██████	██████	██████	██████	██████
Total cost of HZ/su vaccine to NIP for 80+ years old population group							
Catch-up	██████	██████	██████	██████	██████	██████	██████
Total cost of HZ/su vaccine to for all age groups							
TOTAL	██████	██████	██████	██████	██████	██████	██████
Net cost of HZ/su vaccine to NIP for 60+ years old population group							
Base case	██████	██████	██████	██████	██████	██████	██████
Catch-up	██████	██████	██████	██████	██████	██████	██████
Total	██████	██████	██████	██████	██████	██████	██████
Net cost of HZ/su vaccine to NIP for 70+ years old population group (net of live-HZ vaccine costs)							
Catch-up	██████	██████	██████	██████	██████	██████	██████
Net cost of HZ/su vaccine to NIP for 80+ years old population group							
Catch-up	██████	██████	██████	██████	██████	██████	██████
Net cost of HZ/su vaccine to for all age groups							
TOTAL	██████	██████	██████	██████	██████	██████	██████

HZ/su: recombinant varicella zoster vaccine; MBS: Medicare Benefits Scheme; NIP: National Immunisation Program
 Source: Section 4_Shingrix BIM_workbook.xlsx from sheet "BIM Results". On Sheet "Vaccine Price" Admin Costs = \$0. On Sheet "Vaccine Uptake" uptake in year 6 for 70 and 80 year olds = 0%. On Sheet "Catchup" uptake in year 6 for 70 and 80 year olds = 0%. The cost of the catch-up program for 61-69 year olds was estimated by subtracting the cost of the program if only 60 year olds were vaccinated from the cost of the base case + catch-up program for 60-69 year olds from the "BIM Results sheet".

The redacted table shows that at Year 5, the estimated number of scripts dispensed for each age cohort ranged from 100,000 – 200,000 per year to over 200,000 per year, and the net financial implication to the NIP across all age groups would be more than \$100 million per

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year.

- 6.57 A comparison of the numbers of individuals treated and the cases of HZ and PHN predicted to be avoided using incidence rates from MacIntyre 2015/BEACH and the ZOE trials, based on the financial estimates provided in the submission, are presented in the table below. The ESC noted the variation in the incidence of HZ and PHN, depending on the data source used.

Table 20: Expected number of cases of HZ and PHN expected to be avoided, using MacIntyre and ZOE trial

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of individuals vaccinated with the HZ/su vaccine						
60 year old program	91,904	93,327	96,646	97,091	97,301	96,527
61-69 year catch-up	701,954	293,259	103,415	80,488	60,795	-
70-79 year catch-up	351,288	214,430	151,019	144,556	141,971	-
80+ year catch-up	342,537	187,939	116,655	113,516	107,888	-
Difference in HZ cases (MacIntyre), 60 year old program only						
60 years old	-1,010	-2,013	-3,018	-3,992	-4,920	-5,791
Difference in HZ+PHN cases (MacIntyre), 60 year old program only						
60 years old	-178	-355	-533	-704	-868	-1,022
Difference in HZ cases (MacIntyre), with catch-up programs						
60- 69 years old	-8,722	-20,000	-30,993	-41,223	-50,214	-57,195
70-79 years old	-2,491	-4,189	-5,359	-6,440	-7,476	-6,983
80+ years old	-4,069	-9,287	-14,145	-18,549	-22,392	-24,341
Difference in HZ+PHN cases (MacIntyre), with catch-up programs						
60- 69 years old	-1,539	-3,529	-5,469	-7,275	-8,861	-10,093
70-79 years old	-217	-411	-551	-681	-806	-516
80+ years old	-1,430	-3,263	-4,970	-6,517	-7,868	-8,552
Difference in HZ cases (ZOE), 60 year old program only						
60 years old	-918	-1,834	-2,752	-3,646	-4,500	-5,305
Difference in HZ+PHN cases (ZOE), 60 year old program only						
60- 69 years old	-25	-50	-75	-100	-123	-145
Difference in HZ cases (ZOE), with catch-up programs						
60- 69 years old	-7,931	-18,210	-28,258	-37,639	-45,919	-52,393
70-79 years old	-1,498	-2,537	-3,263	-3,939	-4,593	-4,269
80+ years old	-2,882	-6,601	-10,092	-13,286	-16,102	-17,589
Difference in HZ+PHN cases (ZOE), with catch-up programs						
60- 69 years old	-217	-499	-774	-1,031	-1,258	-1,435
70-79 years old	-77	-146	-197	-245	-291	-191
80+ years old	-331	-757	-1,158	-1,525	-1,848	-2,018

Source: Section 4_Shingrix BIM_workbook.xlsx from sheet "Summary". On Sheet "Vaccine Uptake" uptake in year 6 for 70 and 80 year olds = 0%. Disease Incidence on the "Model Inputs" sheet was changed as per Table 1.

Quality Use of Medicines

- 6.58 The submission stated that comprehensive educational activities supporting the quality use of vaccines to ensure healthcare professionals and HZ/su vaccine recipients were educated on the importance of completing the two-dose course were planned.
- 6.59 The submission did not indicate whether any post-market surveillance would be carried out. Given the expected extensive use of the HZ/su vaccine in the routine and

catch-up programs this may be informative, particularly the reporting of adverse events as this is a new vaccine and with a previously un-used adjuvant in Australia.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of the varicella zoster virus vaccine (HZ/su) on the National Immunisation Program (NIP) for the prevention of herpes zoster 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, that the incremental cost-effectiveness ratios (ICER) were highly uncertain and that the estimated financial impact was high and uncertain. Given the large opportunity cost, the PBAC considered more conservative cost-effectiveness analyses were required.
- 7.2 The PBAC noted that the submission did not include an evaluation of NIP-funded HZ/su vaccine at a lower age threshold of at least 50 years, as was recommended in the ATAGI pre-submission advice, for: (i) Indigenous individuals (who have a greater burden of disease); or (ii) people who are immunocompromised as a result of underlying medical conditions or treatment who cannot receive the live-HZ vaccine (unmet need). The PBAC also noted that HZ/su vaccination in immunocompromised individuals was identified by the sponsor as the subject of future regulatory submissions (pre-Sub-Committee Response).
- 7.3 The PBAC noted the submission proposed no vaccine as the comparator for individuals aged 60-69 years and 80+ years, and the live-HZ vaccine for individuals aged 70-79 years. The comparisons presented in the submission did not enable the PBAC to consider the most appropriate age for HZ/su vaccination. To assess the cost-effectiveness of the proposed program, the PBAC considered that an analysis comparing the HZ/su vaccine in 60 year old individuals with the live-HZ vaccine in 70 year old individuals would be required. Further, the vaccination age is likely to impact uptake. Based on the estimates presented in the submission, uptake in 60 year olds was substantially lower than in 70 year olds (31% versus 49%). The PBAC noted vaccination at age 65 years, which would align with the age for influenza vaccination, may increase uptake rates. In addition, a separate cost-effectiveness analysis for the proposed five-year catch-up program would be required.
- 7.4 The PBAC noted that the submission was based on two large, multicentre, randomised trials comparing two doses of HZ/su to placebo (ZOE-50 and ZOE-70) and an indirect comparison comparing two doses of HZ/su to the single dose of live-HZ vaccine, using placebo as the common comparator (pooled results for individuals aged 70 years and over from ZOE-50 and ZOE-70 versus SPS).
- 7.5 The PBAC considered that the clinical trials demonstrated the superior effectiveness of the HZ/su vaccine compared to placebo in individuals aged 60-69 years and 80+ years. The PBAC considered that the evidence demonstrated the superior effectiveness of the HZ/su vaccine compared to the live-HZ vaccine in individuals aged

70-79 years. However, the PBAC considered that the magnitude of benefit of the HZ/su vaccine in both comparisons was uncertain as:

- The ZOE-50 and ZOE-70 trials excluded individuals who had previously received the live-HZ vaccine, who had previously had herpes zoster or who were immunocompromised or immunosuppressed. Accordingly, the PBAC considered that the efficacy of the HZ/su vaccine may be lower in the NIP population compared to the ZOE trial populations; and
- Vaccine efficacy in the trials was reliant on the individual receiving two doses of HZ/su, two months apart. The PBAC were concerned that the proportion of individuals receiving the two doses may be reduced in a population program compared to the clinical trial setting, particularly considering the relatively high rate of reactogenicity associated with the HZ/su vaccine in the seven days post the first dose (9.0% of 60-69 year olds reported a Grade 3 reaction). The duration of protection after a single dose of HZ/su was unknown.

- 7.6 The PBAC noted that there was limited data to assess waning of the HZ/su vaccine and the longer-term need for a booster. Although, as advised by the ESC, waning of the HZ/su vaccine would likely take many years for the primary cohort of 60 year olds, the PBAC considered that there would likely be a loss of protection during an individual's lifetime. The PBAC noted the rate of waning was an important consideration for changing the age of vaccination from 70 to 60 years.
- 7.7 The PBAC considered the claim of non-inferior safety to the live-HZ vaccine and 'slightly' inferior safety to placebo was acceptable, noting the increased frequency of injection site reactions compared to placebo.
- 7.8 The PBAC noted that separate economic analyses were presented for individuals vaccinated at 60 years (versus no vaccine), at 70 years (versus live HZ vaccine) and at 80 years (versus no vaccine). These analyses did not enable a comparison of the proposed program (vaccination at 60 years with a five-year catch-up program in individuals aged ≥ 61 years) and current vaccination program (vaccination at 70 years with five-year catch-up in individuals aged 71-79 years). These analyses also did not consider vaccination in those previously vaccinated with the live-HZ vaccine.
- 7.9 The PBAC noted that BEACH data, at the recommendation of ATAGI, was used to estimate baseline incidences of herpes zoster and post-herpetic neuralgia in the economic model. The PBAC noted that the incidence rates in the placebo arms of the ZOE trials were considerably lower. The PBAC considered, as the trial populations were reasonably similar to the Australian population and would have received active monitoring for herpes zoster and post-herpetic neuralgia, that the magnitude of this difference could not be explained by the exclusion criteria of the trials. The PBAC considered that a more conservative estimate of the incidences of herpes zoster and post-herpetic neuralgia should be used.
- 7.10 The PBAC noted that the submission assumed HZ/su vaccine efficacy declined slowly

over time. For an individual vaccinated at 60 years, the model assumed a 1% annual decline in efficacy during for the first four years post vaccination, 2.3% annual decline in efficacy until the age of 70 (i.e. 10 years post immunisation) and a 3.6% annual decline thereafter, which resulted in a 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 were uncertain and optimistic. The PBAC noted that the ATAGI supported vaccine efficacy, based on immunogenicity data, for up to at least nine years and stated that reliable estimation of waning beyond four years was not currently possible. The ATAGI also noted a recent American study (Le, 2018) that assessed the cost-effectiveness of HZ/su compared to the live-HZ vaccine and which used a base case assumption of 5.4% waning per year, based on SPS trial data, for both vaccines. This resulted in a duration of vaccine protection of 19.3 years following immunisation at 60 years. The PBAC noted that this study assumed a rate of waning for single dose HZ/su to be twice that for two doses (i.e. 10.8%). The PBAC considered that more conservative assumptions regarding waning than used in the submission would be appropriate. The PBAC noted that the rate of waning was an important consideration for determining the appropriate vaccination age.

- 7.11 The PBAC noted that in the analyses of individuals aged 70 years, the model assumed that the cost of the live-HZ vaccine would be replaced, resulting in an ICER of \$15,000 - \$45,000. However, the proposed NIP listing for the HZ/su vaccine allows for re-vaccination of individuals who have received the live-HZ vaccine. The PBAC considered, given the improved effectiveness of the HZ/su vaccine, that individuals would be re-vaccinated. The PBAC noted that the ICER presented in the PSCR, that adopted the ATAGI advice suggesting a re-vaccination program with HZ/su five years after the initial vaccination with the live-HZ vaccine, was \$15,000 - \$45,000 (this ICER could not be verified, as the model provided with the submission did not allow revaccination to be addressed). The PBAC considered that re-vaccination after five years was appropriate, with sensitivity analyses provided for re-vaccination at shorter intervals.
- 7.12 Overall, the PBAC considered that the economic model included in any future re-submission should enable a comparison of vaccinating at different ages and re-vaccination, as well as more conservative assumptions regarding:
- The incidences of herpes zoster and post-herpetic neuralgia without vaccination;
 - The rate of waning used from Year 5 onwards; and
 - The proportion of individuals receiving both doses of HZ/su and the vaccine efficacy associated with receiving one dose only.
- 7.13 The PBAC agreed with the ESC that, although subsidisation of HZ/su would provide direct benefits to the treated individual, it was concerned about the high opportunity costs. The threshold of incremental QALYs gained for treatments with large opportunity costs, such as population preventative interventions including lipid-

lowering, anti-hypertensive drugs and vaccines, was at the lower end of the ICER range. The PBAC considered that the ICERs proposed in the submission were highly uncertain and suggested that lower ICERs would be more appropriate.

- 7.14 The PBAC considered that the assumption that 80% of individuals aged 61 years and over would receive the HZ/su vaccine during the five-year catch-up program was optimistic. The PBAC considered that more accurate estimates, which separately considered the vaccination of 60 year olds replacing the current 70 year old program with the live-HZ vaccine, the five year catch-up program for those aged 61 years and over and those re-vaccinated following vaccination with the live-HZ vaccine would be informative.
- 7.15 The PBAC considered that any future re-submission would need to be a major submission to address the cost-effectiveness concerns and provide more accurate financial estimates.
- 7.16 The PBAC noted that this submission is not eligible for independent review, as independent review is only applicable for submissions requesting PBS listing.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Shingrix is a significant scientific advancement in the field of vaccinology, demonstrating unprecedented efficacy against shingles of greater than 90% in the 50 year and above population studied. It is a cost-effective intervention that brings a clear benefit for a broad population, which is evidenced by the strong and broad recommendations that have been made in other countries that have considered adding *Shingrix* to their vaccination programs, including the US, Canada and Germany. Though GSK is disappointed with the PBAC decision not to recommend *Shingrix* for inclusion into the Australian National Immunisation Program, we take note of the advice. In addition, GSK strongly believes it is important that the full value of vaccination at a societal level be recognized through the evaluation process. This is a topic where more dialogue will be required with the PBAC.