7.9 ZOSTER VIRUS VACCINE LIVE 0.65 mL injection, prefilled syringe; Zostavax®; bioCSL (Australia) Pty Ltd.

1 Purpose of Application

1.1 The re-submission requested a listing on the National Immunisation Program (NIP) for an ongoing cohort of immunocompetent people aged 70, as well as a 71-79 year old catch-up cohort. This fourth re-submission changed the target population for the requested listing to an older cohort from that originally specified; which was an ongoing immunocompetent cohort of people aged 60 and a catch up cohort of 61-79 year olds.

1.2 The change of target population was supported by a comparison of the relative and absolute effects of the vaccine in the Shingles Prevention Study (SPS). While vaccine efficacy in terms of reducing zoster is lower in the 70+ year old cohort than the 60-69 year old cohort, it does not appear to be so in terms of reducing post herpetic neuralgia (PHN). A greater number of zoster cases are avoided in the younger cohort but this is offset by a larger absolute difference in PHN in the older age group and the PHN health state attracts a higher disutility than does zoster in the economic model (table below).

Relative versus absolute effects in the SPS trial across age cohorts

Age cohort (years)	RRR (or vaccine efficacy)	Absolute difference (cases per 1000 person years)
Zoster		
60-69	63.9%	-6.90
70+	37.6%	-4.32
PHN		
60-69	65.6%	-0.49
70+	66.8%	-1.42

SPS = Shingles Prevention Study; RRR = relative risk reduction; PHN = post herpetic neuralgia
Source: Table B.3.1, p38 and Table B.3.2, p41 of the resubmission. Numbers calculated during the evaluation.

2 Requested listing

2.1 Listing was sought for the following cohorts of immunocompetent persons:

- Ongoing cohort of 70 year old individuals
- Catch-up cohort for individuals aged 71-79 years

Name, Restriction, Manner of administration and form	Max. Qty	Proprietary Name and Manufacturer	
ZOSTER VIRUS VACCINE, LIVE, SUBCUTANEOUS INJECTION (REFRIGERATED FORMULATION) 0.65ML (WHEN RECONSTITUTED) CONTAINING A MINIMUM DOSE OF 19,400 PLAQUE-FORMING UNITS	1	Zostavax	bioCSL

2.2 The requested price for zoster vaccine is $[redacted]/dose for all patients, the same as offered in the pre-PBAC response in March 2014, and reduced from $[redacted]/dose for the 60 year old ongoing cohort and $[redacted]/dose for the catch-up cohort for individuals aged 61-79 years in the previous main re-submission in March 2014.

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

3 Background

3.1 Zoster vaccine was TGA registered in 2007 for the prevention of herpes zoster, prevention of PHN and for reduction of acute and chronic zoster-associated pain in individuals 60 years of age and older. In a subsequent application (2013), the TGA indication was broadened to include the prevention of herpes zoster in patients 50 years and older.

3.2 Zoster vaccine had been considered four times previously by the PBAC. The first submission was in July 2007 for the November 2007 PBAC meeting. A minor re-submission was made in December 2007 for the March 2008 PBAC meeting, at which Zostavax was recommended for listing. PBAC subsequently reviewed its decision to list zoster virus vaccination in line with standard practice for recommendations that are more than 5 years old and have not been implemented. At the July 2013 PBAC meeting the Australian Technical Advisory Group on Immunisation (ATAGI) identified key model inputs that may have changed since the 2008 recommendation and may affect the estimation of cost effectiveness. A resubmission was evaluated for the March 2014 PBAC meeting. The pre-PBAC response revised the proposed listing to suggest targeting a 70 year old ongoing cohort and 71-79 year old catch-up cohort and presented an economic model for the revised listing. At the March 2014 meeting the PBAC deferred its decision on Zoster Vaccine and considered that a major submission to the PBAC was required to determine cost-effectiveness of zoster vaccine in the 70 year old cohort.

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

4 Clinical place for the proposed therapy

4.1 Zoster vaccine is used to prevent zoster and the complications of zoster (i.e. PHN). The clinical management of zoster / PHN remains the same, irrespective of whether the person has been vaccinated or not.

4.2 The post-submission ATAGI advice stated that ATAGI had revised its recommendation regarding the concomitant administration of Zostavax with the pneumococcal vaccine, Pneumovax 23 (23vPPV). ATAGI now considers it acceptable to administer Zostavax and 23vPPV concomitantly. This revision was based primarily on post-licensure data that showed that immunogenicity was similar when Zostavax was administered simultaneously with 23vPPV or 4 weeks apart. Of note the USA Advisory Committee on Immunization Practices (ACIP) and the UK Joint Committee on Vaccination and Immunisation (JCVI) also recommend co-administration of Zostavax and 23vPPV for eligible adults. It is anticipated that this would simplify the implementation of the proposed Zostavax vaccination program.

This recommendation is still preliminary and requires public consultation and endorsement from the NHMRC, prior to inclusion in The Australian Immunisation Handbook, which is anticipated to occur in mid-2015.

4.3 ATAGI reiterated that if Zostavax is included on the NIP it is essential to establish a dedicated vaccination register that captures population-based data on vaccination in adults. There is no systematic means to capture validated national data on the uptake of vaccines currently funded under the NIP in older persons in Australia (influenza and pneumococcal vaccines). In addition, as recommended in the NHMRC-endorsed Australian Immunisation Handbook (10th Edition 2013), there are an increasing number of vaccines recommended for use in adolescents and adults in recent years, leading to confusion and difficulty in recall regarding vaccination history for both patients and providers, as the current Australian Childhood Immunisation Register (ACIR) does not record vaccinations beyond 7 years of age, and the HPV Vaccine Register is vaccine specific, and managed by the Cervical Cancer Registry. Accurate recording of vaccine administration is essential to optimize vaccine provision for effective disease prevention, to avoid repeat vaccination, under-vaccination, and vaccine wastage and leakage. ATAGI considers that an immunisation register is also an essential requirement to enable robust assessment of vaccination program impact, particularly for Zostavax. Given the uncertainty around Zostavax vaccine effectiveness and duration of protection against both herpes zoster and post-herpetic neuralgia, the potential need for additional changes in policy and practice in the future (e.g. need for a booster dose) and the importance of monitoring vaccine safety, a register that allows access to data at both the individual patient/provider level and at a population level is a requirement.

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

5 Comparator

5.1 The comparator is standard medical management of patients with zoster / PHN. This comparator has been accepted by the PBAC.

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 discussed some aspects of uncertainty in the submission, including the incidence of zoster in Australia, the proportion of PHN in patients with zoster, the quality of life impact of PHN and addressed other matters in response to the Committee's questions.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (4), a health care professional (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of zoster virus vaccine,

including the potential prevention of pain and reduced quality of life, reduced burden to patients and families, and the need for the vaccine to be affordable.

Clinical trials

6.3 The re-submission was based on one head-to-head trial (SPS) of zoster vaccine compared with placebo and two extension studies (Short-Term Persistence Substudy (STPS) and the single arm Long Term Persistence Study (LTPS)). The clinical evidence was unchanged from the March 2014 re-submission. No new data cut-offs for these studies were available; however, unlike the previous submission, the results have been presented according to 5 or 10 year age brackets wherever possible. This was requested by the PBAC in the 7.9 PBAC Ratified Minutes, March 2014.

6.4 Although the evidence base for the new submission remained unchanged, the requested target population was changed from an ongoing cohort of 60 year old patients to 70 year old patients. Consequently, the most appropriate estimates from the key studies are the modified ITT results (the mean age at vaccination in the SPS is 69.4 years).

6.5 Details of the trials presented in the re-submission are reproduced below.

Trials and associated reports considered by the PBAC

Trial	Reports	Publication citation
SPS (Protocol 004)	MRL Clinical Study Report, Multicenter Study: Trial of Varicella Zoster Vaccine for the Prevention of Herpes Zoster and its Complications (includes Adverse Event Monitoring (AEM) Substudy and The Cell Mediated Immunity (CMI) Substudy) Publications: Oxman, M. N., Levin, M. J., Johnson, G. R., et al. A vaccine to prevent herpes zoster and post-herpetic neuralgia in older adults Oxman, M. N. and Levin, M. J. Vaccination against Herpes Zoster and Postherpetic Neuralgia Levin, M. J., Oxman, M. N., Zhang, J. H., et al. Varicella-zoster virus-specific immune responses in elderly recipients of a herpes zoster vaccine Weinberg, A., Zhang, J. H., Oxman, M. N., et al. Varicella-zoster virus-specific immune responses to herpes zoster in elderly participants in a trial of a clinically effective zoster vaccine Schmader, K. E., Johnson, G. R., Saddier, P., et al. Effect of a Zoster Vaccine on Herpes Zoster-Related Interference with Functional Status and Health-Related Quality-of-Life Measures in Older Adults Simberkoff, M. S., Arbeit, R. D., Johnson, G. R., et al. Safety of herpes zoster vaccine in the shingles prevention study: a randomized trial Irwin, M. R., Levin, M. J., Laudenslager, M. L., et al. Varicella zoster virus-specific immune responses to a herpes zoster vaccine in elderly recipients with major depression and the impact of antidepressant medications	March 2005 N Engl J Med 2005; 352(22): 2271-84 J Infect Dis 2008; 197 (Suppl 2): S228-36 J Infect Dis 2008; 197(6): 825-35 J Infect Dis 2009; 200(7): 1068-77 J Am Geriatr Soc 2010; 58(9): 1634-41 Ann Intern Med 2010; 152(9): 545-54 Clin Infect Dis 2013; 56(8): 1085-93
STPS (Protocol 004 X1)	Clinical Study Report: Trial of Varicella Vaccine for Herpes Zoster and its Complications Persistence Substudy Publication: Schmader, K. E., Oxman, M. N., Levin, M. J., et al. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy	June 2008 Clin Infect Dis 2012; 55(10): 1320-8
LTPS (Protocol 013)	Clinical Study Report: Long-Term Persistence of Zoster Vaccine (ZOSTAVAX) Efficacy in Subjects 60 Years of Age and Older Publication: Morrison, V. A., Johnson, G. R., Schmader, K. E., et al. Long-Term Persistence of Zoster Vaccine Efficacy	March 2012 Clin Infect Dis 2014; doi:10.1093/cid/ciu918
SPS (Protocol 004 V1)	Clinical Study Report: Trial of Varicella-Zoster Vaccine for the Prevention of Herpes Zoster and Its Complications - Administration of Investigational Live Attenuated Zoster Vaccine to Shingles Prevention Study Placebo Recipients (Protocol 004-08)	October 2008

Source: Reproduced from the PBAC 03-2014 minutes for 7-9 Zoster Virus Vaccine.

6.6 The key features of the included evidence are provided below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Zoster virus vaccine versus placebo						
Protocol 004	38,546	R, DB, MC	Low	≥60 years, mean age = 69.4 years immunocompetent	Reduction in incidence of zoster, PHN and burden of illness (vaccine efficacy)	Vaccine efficacy in terms of reduction in the incidence of zoster and PHN from the overall population used
Protocol 004 X1	14,270	Extension	The ESC* considered the bias was moderate	Enrolled in Protocol 004	As above	As above
Protocol 013	6,867	Extension SA, OL	High	Vaccine recipient in Protocol 004 or 004 X1	As above	As above

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised; SA=single arm.
*ESC advice for the March 2014 PBAC meeting.
Source: Compiled during the evaluation

Comparative effectiveness

6.7 The estimated efficacy of the vaccine at reducing the incidence of zoster remains unchanged. It is summarised in the table below. The analyses presented for the first time in the re-submission are in bold font. These additional analyses are exploratory, post hoc subgroup analyses. The results indicate that vaccine efficacy, in terms of reducing zoster incidence, is age-dependent. Vaccine efficacy also appears to wane over time. The rate of waning in vaccine efficacy at reducing zoster incidence in the 70+ year age group cannot be determined due to the small number of cases in the subgroups.

6.8 The PBAC was concerned (as per para 6.8 Zoster Virus Vaccine ratified March 2014 PBAC minutes) that the point estimate of vaccine efficacy in the initial period of LTPS (between Year 6 and Year 8) was higher than the vaccine efficacy of the STPS (Year 4-6). The PBAC considered that this increasing vaccine efficacy after vaccination was counter-intuitive and inconsistent with the observed waning efficacy against zoster. This concern has not been resolved.

Incidence of zoster in the SPS, STPS and LTPS

Age strata	Age group	ZOSTAVAX (N = 19,270)			Placebo (N = 19,276)			Vaccine Efficacy % (95% CI)
		Number subjects	Zoster cases	Incidence/ 1,000 person yrs	Number subjects	Zoster cases	Incidence/ 1,000 person yrs	
SPS								
Full	60+	19,254	315	5.415	19,247	642	11.119	51.3% (44.2, 57.6)
Pre-spec'd	60-69	10,370	122	3.895	10,356	334	10.791	63.9% (55.5, 70.9)

	70+	8,884	193	7.180	8,891	308	11.500	37.6% (25.0, 48.1)
10 years	60-69	10,370	122	3.895	10,356	334	10.791	63.9% (55.5, 70.9)
	70-79	7,621	156	6.736	7,559	261	11.388	40.8% (27.6, 51.8)
	80+	1,263	37	9.944	1,332	47	12.164	18.3% (-28.5, 48.3)
5 years	**60-64**	[redacted]						
	65-69							
	70-74							
	75-79							
STPS								
Full	60+	7,320	84	8.430	6,950	95	13.967	39.6% (18.2, 55.5)
Pre-spec'd	60-69	[redacted]						
	70+*							
10 years	60-69							
	70-79							
LTPS								
Full	60+	6,867	261	10.337	Method III		14.126	26.8% (17.4, 35.4)
Pre-spec'd	60-69	[redacted]						
	70+							

The analyses presented for the first time in the re-submission are bolded.
Full = Full trial population, which is actually the MITT population: all subjects randomised who were followed for at least 30 days post-vaccination and did not develop evaluable zoster within the first 30 days post-vaccination.
Pre-spec'd = the pre-specified age group analysis; 10 years = analysis by ten-year age band; 5 years = analysis by five-year age band; Method III = Method used to estimate historical control rates, where zoster incidence is calculated from SPS+STPS adjusting for age and calendar effect. This method estimates the vaccine efficacy that is higher than the other two methods and is therefore the least conservative. Vaccine efficacy for Method I is estimated at 20.2% and 22.4% for 60-69 years and 70+ years age groups and for Method II vaccine efficacy is [redacted]% and [redacted]% for 60-69 years and 70+ years age groups respectively.
* The pre-specified subgroup of 70+ years had an estimated vaccine efficacy of [redacted]%, as there were [redacted] additional cases of zoster in the 80+ years age group in the vaccine arm and only [redacted] additional case in the 'no vaccine' arm. This may be an indication of variability due to small numbers of zoster cases, a lack of vaccine efficacy in people older than 80 years, or both.
Source: Table B.3.1, Section B July 2014 Resubmission

6.9 The estimates of vaccine efficacy in reducing the incidence of PHN remain unchanged and are summarised in the table below. Analyses presented for the first time in the re-submission are highlighted in bold font. The re-submission claims that efficacy of the vaccine in reducing PHN is not age-dependent and that there is similar initial vaccine efficacy across age groups. The interpretation of vaccine efficacy

results in terms of PHN needs to take account of the very small number of PHN cases. As a consequence, in the exploratory subgroup analysis, initial vaccine efficacy in the different age groups is variable and likely unreliable. The re-submission acknowledged that the efficacy of the vaccine as measured by reduction in the incidence of PHN wanes over time.

6.10 The ESC noted that the PBAC at the March 2014 meeting raised concerns about the results from the LTPS as it used the most favourable model to predict the placebo response and therefore the effectiveness is likely to be overestimated. As no new data were presented, the ESC considered that this is still the case for the estimate of the effectiveness of the LTPS.

Incidence of PHN in the SPS, STPS and LTPS

Age strata	Age group	ZOSTAVAX (N = 19,270)			Placebo (N = 19,276)			Vaccine Efficacy % (95% CI)
		Number subjects	PHN cases	Incidence/ 1,000 person yrs	Number subjects	PHN cases	Incidence/ 1,000 person yrs	
SPS								
Full	60+	19,254	27	0.464	19,247	80	1.384	66.5% (47.5, 79.2)
Pre-spec'd	60-69	10,370	8	0.255	10,356	23	0.743	65.6% (20.4, 86.7)
	70+	8,884	19	0.707	8,891	57	2.128	66.8% (43.3, 81.3)
10 years	60-69	[redacted]						
	70-79							
	80+							
5 years	**60-64**							
	65-69							
	70-74							
	75-79							
STPS								
Full	60+	7,320	7	0.704	6,950	12	1.764	60.1% (-9.8, 86.7)
Pre-spec'd	60-69	[redacted]						
	70+*							
10 years	60-69							
	70-79							
LTPS	LTPS							
Full	60+	6,867	32	1.267	Method III		1.892	33.0% (5.4, 54.2)
Pre-spec'd	60-69	[redacted]						
	70+							

Analyses presented for the first time in the re-submission are highlighted in bold text.
Full = Full trial population; Pre-spec'd = the pre-specified age group analysis; 10 years = analysis by ten-year age band; 5 years = analysis by five-year age band; Method III = Method used to estimate historical control rates, where PHN incidence is calculated from SPS and STPS adjusting for age.
*The pre-specified subgroup of 70+ had an estimated vaccine efficacy of [redacted]%, as there were [redacted] additional cases of zoster in the 80+ age group in the vaccine arm and [redacted] in the 'no vaccine' arm.
Source: Table B.3.2, Section B July 2014 Resubmission

Comparative harms

6.11 The re-submission provided safety data, from an adverse event monitoring substudy

(a subgroup of the SPS) and the Pre-Sub-Committee Response (p1) provided safety data from the full SPS population, both stratified by age. The ESC noted that there were no serious vaccine-related adverse events in the immunised cohort.

Benefits/harms

6.12 A summary of the comparative benefits and harms for zoster vaccine versus placebo is presented in the table below.

Summary of comparative benefits and harms for zoster vaccine and placebo from the overall population of SPS, STPS and LTPS

	N	Vaccine efficacy (95%CI)[c]	Event rate/1000 person years		Increment (pyr)
			Zoster vaccine	Placebo	
Benefits					
Reduction in zoster					
SPS	38,492	51.3% (44.2, 57.6)	5.42	11.12	-5.7
STPS	14,270	39.6% (18.2, 55.5)	8.43	13.97	-5.5
LTPS (Method 3)	6,867	26.8% (17.4, 35.4)	[redacted]	[redacted]	[redacted]
Reduction in PHN					
SPS	38,492	66.5% (47.5, 79.2)	0.46	1.38	-0.9
STPS	14,270	60.1% (-9.8, 86.7)	0.70	1.76	-1.1
LTPS (Method 3)	6,867	33.0% (5.4, 54.2)	[redacted]	[redacted]	[redacted]
	N	**RR (95%CI)**	**Event rate (%)[b]**		**RD (%)**
			Zoster vaccine	**Placebo**	
Harms					
Injection site adverse event (AEMS)	6,616	2.91 (2.67, 3.17)	48.3	16.6	31.7 (29.6, 33.8)
Allergic reactions (VSD)	193,083	2.13 (1.87, 2.40)	0.13[a]	-	-

Source: Table 5, p8 of the Commentary for March 2014 PBAC meeting and Table B.3.5, p47 of the re-submission.
VSD = Vaccine Safety Datalink; AEMS = adverse event monitoring substudy of Protocol 004 (presented in previous submission); pyr = person years; RR = risk ratio; RD = risk difference
[a] Event rate is 257 patients (of 193,083) that had an allergic reaction during 7 days following vaccination.
[b] AEMS reported adverse events in the 42 days following vaccination. VSD reported allergic reactions that occurred in the 7 days following vaccination.
[c] Vaccine efficacy is 1 minus the relative risk reduction * 100%.
Method 3 uses data from SPS and STPS and adjusts for age and calendar effects for zoster and for age effects only for PHN to estimate the control rate.
Increment is the difference between the event rates per 1000 person years. Note that in these trials only the first zoster case per person was counted.

6.13 Assuming vaccine efficacy is maintained for 10 years (the duration suggested in the evaluation based on the approximate duration of the SPS, STPS and LTPS combined), the evidence presented in the re-submission suggests that for every 1000 people (ITT) receiving zoster vaccination, compared with those who are unvaccinated:

- Between 38 and 57 more people would avoid a case of zoster; and
- Between 6 and 11 more people would avoid a case of PHN.

On the basis of evidence presented in the re-submission, in the 42 days following zoster vaccination, for every 1000 people receiving zoster vaccination, compared with those who are unvaccinated:

- 320 more people would experience an injection site adverse event (ITT);

Clinical claim

6.14 A clinical claim was not stated in the re-submission. The presented evidence supported a claim that zoster vaccine is superior to placebo in terms of reducing the incidence of zoster and PHN and inferior to placebo in terms of comparative safety for the target cohort of people aged 70 years and a catch up cohort aged 71-79 years. The ESC noted that the vaccine was not as effective in the 70-79 age group compared to 60-69 age group for reducing incidence of zoster, but this reduction was offset by a greater reduction in PHN in the older group. Overall, the ESC considered that the vaccine is effective and probably more effective in the older age group with acceptable safety.

6.15 In the post-submission advice, ATAGI maintained that "it is reasonable to assume that the initial vaccine efficacy of Zostavax would decrease with increased age. ATAGI reiterates that it is highly likely that Zostavax vaccine efficacy could wane at a faster rate in those vaccinated at an older age compared with a younger age…. ATAGI considers that it is particularly difficult to confidently derive vaccine efficacy estimates for single-year age groups from the available clinical trial data over time, and notes that uncertainty relating to age-specific initial vaccine efficacy and rate of waning remains…. With regard to waning, ATAGI notes that a recent summary statement on herpes zoster vaccination from the USA Advisory Committee on Immunization Practices (ACIP) concluded, based on all available evidence, that vaccine efficacy of Zostavax for preventing HZ [zoster] in persons ≥60 years of age beyond year 5 remains uncertain. ACIP also highlighted that Zostavax vaccine efficacy estimates against PHN (although having point estimates that were higher than that for HZ) were not statistically significantly different from zero from year 3 onwards".

Economic analysis

6.16 The submission presented a cost-utility analysis. The model structure, time horizon, outcomes measured and methods used to generate the results (table below) remained unchanged from the model in the submission considered at the March 2014 PBAC meeting. A number of key variables from the previous re-submission were updated, including an updated price, and vaccine efficacy in terms of a reduction of the incidence of zoster (+/- PHN) and severity and duration of zoster (+/- PHN).

Summary of model structure and rationale

Time horizon	Until patients are 105 years. This equates to 35 years of follow-up for a 70 year old cohort in the model. There were up to 7 years follow up for the pooled results of the SPS and STPS trials.
Outcomes	QALYs
Methods used to generate results	Markov model cohort expected value analysis
Cycle length	1 year
Transition probabilities	Comparator arm: • Zoster - age specific annual incidence rate of zoster (BEACH data); • Age specific annual incidence rate of PHN given zoster (SPS data); • Age specific all-cause mortality (ABS data). Vaccine arm: • Age specific annual incidence rate of zoster (BEACH data) adjusted for the expected vaccine efficacy as observed in the trials, using either trial-based estimates or modelled estimates; • Age specific annual incidence rate of PHN given zoster (SPS) adjusted for the expected vaccine efficacy as observed in the trials, using either trial-based estimates or modelled estimates; • Age specific all-cause mortality (ABS data).
Discount rate	5% for costs and outcomes
Software package	TreeAge Pro 2013

QALYs = quality-adjusted life-years; BEACH = Bettering the Evaluation of Care and Health; SPS = Shingles Prevention Study; STPS = Short Term Persistence Study; ABS = Australian Bureau of Statistics.
Source: Compiled during the evaluation

6.17 The re-submission presented two base case analyses in which vaccine efficacies are estimated using two approaches – trial based estimates and modelled estimates. Truncating the duration of the model reduces some of the potential overestimation of vaccine efficacy from the LTPS period (as discussed above). The economic model (when using trial-based mean vaccine efficacy) is not particularly sensitive to vaccine efficacy in terms of reducing zoster.

6.18 The key drivers of the model are summarised in the table below.

Key drivers of the model

Description	Method/Value	Impact
Incidence of zoster*	Estimated from BEACH data (70-79 years: [redacted]%; 80 + years: [redacted]%) which include immunocompromised people and may be an over-estimate of the true incidence of zoster in the proposed immunocompetent NIP population. This estimate from BEACH data is significantly higher than the incidence observed in the SPS trial (70 + years: 1.1434%).	Moderate (favours vaccine)
Incidence of PHN, given zoster*	Calculated using SPS data for all patients aged over 70 years at vaccination (70-99 years; 18.5%), which is considerably higher than the incidence of PHN observed in the ITT population (mean age at vaccination 69.4 years) of 12.4472%. The estimate used in the base-case of the model is likely to be an overestimate for the 70 year old ongoing cohort.	Moderate (favours vaccine)
Disutility associated with a case of PHN*	Based on the distribution of patients by average pain score in the SPS over time, weighted by the expected QALY loss associated with each of the pain categories from the MASTER study. Non-clinically relevant pain scores have been included. The SPS study results may not be representative, given the very small number of patients being followed beyond the protocol specified period (26 weeks), which appears to drive much of the disutility (e.g. the duration of PHN was some 3.29 years).	Moderate (favours vaccine)
Duration of vaccine efficacy (incidence & severity and duration)	Vaccine efficacy wanes over 13 years in the modelled and trial-based base case models, rather than over 10 years as proposed by ESC for the 60 year old cohort.	Moderate (favours vaccine)
Vaccine efficacy in terms of a reduction in the duration and severity of zoster (+/- PHN)	Vaccine efficacy in term of reduction in disutility: Zoster: [redacted]% PHN: [redacted] The above estimates are derived from the 70-99 year old cohort. This is likely to be an overestimate of the disutility for a 70 year old.	Low (favours vaccine)

*These variables refer to the background incidence and disutility that are applied in the control arm.
Source: compiled during the evaluation

6.19 The results of economic evaluations for the ongoing cohort and catch up cohorts are summarised in the tables below.

Results of the economic evaluation for the ongoing cohort

Vaccination Age	Discounted Incremental cost ($)	Discounted Incremental effectiveness (QALY)	ICER ($/QALY)
Vaccine efficacy: Trial-based estimates			
70	[redacted]	[redacted]	[redacted]
Vaccine efficacy: Modelled estimates			
70	[redacted]	[redacted]	[redacted]
Modelled evaluation for the previous submission (March 2014 PBAC meeting) - 60 year old cohort, price and efficacy of vaccine have been updated			
60	[redacted]	[redacted]	[redacted]

QALY = quality-adjusted life years; ICER = incremental cost effectiveness ratio
Numbers may not be added up due to rounding.
Source: Table D.5.5, Section D, p90 of the re-submission

Results of the economic evaluation for the catch-up cohort

Vaccination Age	Discounted Incremental cost ($)	Discounted Incremental effectiveness (QALY)	ICER ($/QALY)
Vaccine efficacy: Trial-based estimates*			
71	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]
73	[redacted]	[redacted]	[redacted]
74	[redacted]	[redacted]	[redacted]
75	[redacted]	[redacted]	[redacted]
76	[redacted]	[redacted]	[redacted]
77	[redacted]	[redacted]	[redacted]
78	[redacted]	[redacted]	[redacted]
79	[redacted]	[redacted]	[redacted]
Weighted average	[redacted]	[redacted]	[redacted]
Vaccine efficacy: Modelled estimates**			
71	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]
73	[redacted]	[redacted]	[redacted]
74	[redacted]	[redacted]	[redacted]
75	[redacted]	[redacted]	[redacted]
76	[redacted]	[redacted]	[redacted]
77	[redacted]	[redacted]	[redacted]
78	[redacted]	[redacted]	[redacted]
79	[redacted]	[redacted]	[redacted]
Weighted average	[redacted]	[redacted]	[redacted]
Modelled evaluation for the previous submission (March 2014 PBAC meeting) - 61-79 year old cohort, price and efficacy of vaccine have been updated			
61-79	[redacted]	[redacted]	[redacted]

*VE_HZ_option=VE_HZ_Interpolated; VE_PHN_option=VE_PHN_SPS_STPS_LTPS; VE_HZ_duration= VE_PHN_duration=13 years.

**VE_HZ_option=VE_HZ_Model3; VE_PHN_option=VE_PHN_Model3_Truncated.

Source: Table D.5.6, Section D, p91 of the re-submission

6.20 For the trial-based estimates, the ICER for the ongoing 70 year cohort was $15,000/QALY - $45,000/QALY and for the catch-up cohort varied between $15,000/QALY - $45,000/QALY and $15,000/QALY - $45,000/QALY (trial-based estimates). Using the modelled estimate, the ICER for the ongoing 70 year cohort was $15,000/QALY - $45,000/QALY and for the catch-up cohort varied between $15,000/QALY - $45,000/QALY and $15,000/QALY - $45,000/QALY.

6.21 Compared to the March 2014 re-submission, applying the conservative estimates of vaccine efficacy, changing the requested ongoing population from 60 year olds to 70 year olds, and reducing the price of vaccine per dose results in a more favourable ICER for the ongoing cohort compared with that in the previous submission. This improvement is primarily a function of differences between the two cohorts in the no-vaccine arm, including an:

- Increased incidence of zoster ([redacted]% for 60 year olds vs [redacted]% for 70-79 year olds) and PHN (given zoster; 6.9% for 60 year olds vs 18.5% for 70+ year olds);
- Increased severity and duration of zoster (disutility; [redacted] QALYs vs [redacted] QALYs for 60-69 year olds and 70+ year olds, respectively) and PHN

(disutility; [redacted] QALYs vs [redacted] QALYs for 60-69 year olds and 70+ year olds, respectively); and

- Increasing cost associated with a case of zoster (combined with PHN) ($[redacted] for 60-69 year olds vs $[redacted] for 70-79 year olds).

6.22 While the above estimates of background incidence of zoster (+/- PHN) and the disutility associated with a case of zoster (+/- PHN) were applied in the previous submission, limiting the duration of vaccine efficacy to 13 years (base case) or 10 years (sensitivity analysis) meant that many of the differences between the two arms were a result of the underlying burden of zoster disease, which is considerably lower in the 60 year old cohort compared with the 70 year old cohort.

6.23 The PBAC noted the sensitivity analysis based on the following inputs:

- Incidence of zoster in the Australian population: the incidence of zoster estimated from BEACH data for an immunocompetent 70-79 year old cohort is greater that the trial incidence. ATAGI has acknowledged the limitation of the BEACH data and that the estimates are high in comparison to other estimates, but considered they are the best available.
- Proportion of patients with zoster who develop PHN: The SPS estimate is derived from patients aged between 70 and 99 years, and may overestimate the proportion of patients with zoster who develop PHN for the 70 year old cohort. This is significantly higher than the estimate for the SPS ITT population (age at vaccination 60-99 years; mean age 69.4 years; 12.4472%); and
- Disutility associated with a case of zoster (+/- PHN) in the comparator arm: The PBAC recalled that, during the consideration of the submission before the recommendation in 2008, the committee had been concerned about the retrospective data collection in the Canadian MASTER study.

6.24 The table below summarises the results of sensitivity analyses conducted during the evaluation for the key variables.

Key sensitivity analyses conducted during the evaluation[1]

#	Concern / Base case	Sensitivity Analyses	Disc. Incr. Costs ($)	Disc. Incr. Effect. (QALY)	ICER ($/QALY)
Incidence of zoster in the Australian population					
1	Whether the increasing incidence of zoster from BEACH data for the 70-79 year old cohort is appropriate or an over-estimate. Base case: BEACH Data 70-79 years=[redacted]% 80+ years =[redacted]%	Using the estimate of the incidence of zoster from the SPS (70 + years 1.1434%), rather than BEACH Data	[redacted]	[redacted]	[redacted]

#	Concern / Base case	Sensitivity Analyses	Disc. Incr. Costs ($)	Disc. Incr. Effect. (QALY)	ICER ($/QALY)
Proportion of patients with zoster who develop PHN					
2	Proportion of patients with zoster who develop PHN is estimated from SPS data for the 70 + year old cohort (i.e. patients vaccinated between 70-99 years of age). Base case: 18.5%	Reducing the proportion of patients with zoster who develop PHN to the lower bound of the 95% confidence interval from the SPS trial (pooled results for all patients aged over 70 years at vaccination: 15.7058%)	[redacted]	[redacted]	[redacted]
3		Reducing the proportion of patients with zoster who develop PHN to the estimate provided in the ITT population (mean age at vaccination 69.4) of the SPS (12.4472%)	[redacted]	[redacted]	[redacted]
4		Reducing the proportion of patients with zoster who develop PHN to 6.9% (the same proportion that was observed for the 60-69 year old cohort in the SPS) for 70-79 year olds only	[redacted]	[redacted]	[redacted]
Disutility associated with a case of zoster (+/- PHN) in the comparator arm					
5	Estimated based on the distribution of patients by average pain score in the SPS over time, weighted by the expected QALY loss associated with each of the pain categories from the MASTER study. Base case (70 + year olds): Disutility of zoster = [redacted] Disutility of PHN = [redacted]	Reducing the disutility associated with a case of PHN to the lower bound of the 95% confidence interval from SPS (age at vaccination 70-99 years; QALY Disutility = 0.124281067)	[redacted]	[redacted]	[redacted]
6		Reducing the disutility associated with a case of PHN for the 70 year old cohort equal to that estimated for the 60-69 year old cohort (0.1134)	[redacted]	[redacted]	[redacted]

[1] All changes made to the results to the base case using trial-based estimates, and are one-way sensitivity analyses. Source: Compiled during the evaluation

6.25 The PBAC considered that the most uncertain input into the economic model was the duration of vaccine efficacy. The PBAC noted that:

- data was based on the 3.4 years median duration of follow-up for participants in the SPS trial,
- the ACIP (US) concluded vaccine efficacy preventing zoster in persons ≥60 years of age beyond year 5 remains uncertain and vaccine efficacy estimates against PHN were not statistically significantly different from zero from year 3 onwards
- In its Immunisation Statement on varicella and herpes zoster vaccines (2010), which recommended a universal herpes zoster vaccination programme for adults aged 70 years up to and including 79 years, the JCVI (UK) considered the estimated duration of protection was at least 7.5 years.
- The Rapid Relative Effectiveness Assessment by the European Network for Health Technology Assessment (eunethta) stated that vaccine efficacy persists for at least 7 years

- The advice from ATAGI that is highly likely that Zostavax vaccine efficacy could wane at a faster rate in those vaccinated at an older age compared with a younger age (discussed above).

6.26 Overall, the PBAC considered that the estimate of duration of vaccine efficacy in the 70+year old cohort for both prevention of zoster and prevention of PHN should be 7 years to inform the respecified base case. The PBAC noted that this estimate of the duration of vaccine efficacy was lower than the estimates in the re-submission and the range of 10-13 years considered during decision making for the 60 year old ongoing cohort the catch-up cohort for individuals aged 61-79 years in the previous submission.

6.27 Respecifying the trial-based base case model for the ongoing 70 year old cohort, where the duration of vaccine efficacy is 7 years for both prevention of zoster and prevention of PHN resulted in an ICER of around $15,000/QALY - $45,000/QALY. The PBAC considered that even with the price proposed in the re-submission compared to the March 2014 re-submission, zoster virus vaccine live was not acceptably cost-effective for the ongoing 70 year old cohort. The PBAC considered that a price reduction in the order of [redacted]% would be required to give an ICER in a range of $15,000/QALY - $45,000/QALY in the respecified base case.

6.28 The PBAC noted that applying the same duration of vaccine efficacy to the trial-based model for each year of the catch up cohort resulted in ICERs ranging between $15,000/QALY - $45,000/QALY.

6.29 Overall, with the reduction in price, the PBAC accepted that the cost-effectiveness for the ongoing cohort of 70 year old individuals and catch-up cohort for individuals aged 71-79 years was acceptable.

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

Drug cost/patient: $[redacted] in the submission.

6.30 The proposed vaccine cost is $[redacted]/dose/patient.

Estimated PBS usage & financial implications

6.31 This re-submission was not considered by DUSC. The approach taken in the current re-submission remains unchanged from the previous submission.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Uptake of zoster vaccine in the 70 year-old cohort						
70 year-old population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Persons vaccinated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of zoster vaccine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake of zoster vaccine in 70 year-olds who miss vaccination during their 70th year						
Unvaccinated from 70 year-old cohorts (mortality adjusted)		[redacted]	[redacted]	[redacted]	[redacted]	

Uptake amongst unvaccinated						
Persons vaccinated						
Cost of zoster vaccine						
Uptake of zoster vaccine in the catch-up cohort						
Population						
Unvaccinated from previous years (mortality adjusted)	-					
Uptake amongst unvaccinated						
Persons vaccinated						
Cumulative % uptake						
Cost of zoster vaccine						
Total uptake for all cohorts						
Total doses from each cohort						
Total cost of zoster vaccine						
Total savings to PBS (Antivirals)						
Net cost to the PBS / RPBS						
Net increase cost to the MBS						
70 year-old cohort						
70 year-old catch-up						
71-79 catch-up						
Net financial implication for the Australian Government health budget						
70 year-old cohort						
70 year-old catch-up						
71-79 year-old catch-up						
Total						

The redacted table above shows that at Year 5, the estimated total doses from each cohort would be over 200,000 and the total net financial implication for the Australian Government health budget would be $30 - $60 million.

6.32 The cost to Government was estimated to be approximately $ over 5 years. The estimated population does not exclude those who are immunocompromised, although this population is determined to be small by the submission (approximately 1%).

6.33 The post-submission ATAGI advice considered that the steady state vaccine coverage estimate of % for the ongoing vaccination cohort (of 70-year olds) and approximately % overall uptake in the catch-up cohort (of ≥71-year olds) in the resubmission are likely overestimates. ATAGI reiterated that it is more reasonable to expect that steady state vaccination coverage would reach approximately % in the revised target cohorts for ongoing vaccination based on Australian Institute of Health and Welfare adult vaccination survey data for pneumococcal and influenza vaccinations in those aged ≥65 years (2004, 2006 and 2009) and cumulative vaccine coverage estimates of the funded Zostavax vaccination program in the UK.

Financial Management – Risk Sharing Arrangements

[redacted]

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of zoster virus vaccine live on the National Immunisation Program (NIP) for the vaccination of immunocompetent persons aged 70 years, and a catch-up cohort of immunocompetent persons aged 71 to 79 years.

7.2 The PBAC was satisfied that zoster virus vaccine live provides, for some patients, a significant improvement in efficacy over standard medical management of patients with zoster/PHN. The PBAC noted the consumer comments on this item.

7.3 The resubmission's nominated comparator of standard medical management of patients with zoster/PHN was previously accepted by the PBAC.

7.4 The PBAC noted that the clinical trials presented in the resubmission remained unchanged from March 2014, however the requested target population for vaccination had changed. It was also noted that the resubmission presented the results according to 5 or 10 year age brackets wherever possible as requested by the PBAC in March 2014.

7.5 The PBAC noted a clinical claim was not stated in the re-submission. The PBAC recalled from the March 2014 meeting that a claim of superior comparative effectiveness of zoster virus vaccine to placebo was reasonable, noting that the vaccine was not as effective in the 70-79 year age group compared to the 60-69 year age group for reducing incidence of zoster. However, the vaccine appears to be more effective in the reduction of PHN in the 70-79 year age group.

7.6 As previously, the PBAC considered the rate of adverse events was reasonable in the context of vaccination, and that serious adverse events were rare.

7.7 The PBAC recalled in March 2014, that the committee considered that, although some assumptions favoured the vaccine and that certain concerns about the utilities remained from the recommendation in 2008, the variations in the structure of economic model proposed by the commentary of the re-submission, and endorsed by ESC, would be an appropriate base case to present the model inputs appropriate to the 70+ year old cohort.

7.8 The PBAC considered that the duration of vaccine efficacy for zoster and PHN was still unclear and did not accept the 13 year duration proposed in the base case of the re-submission. The PBAC noted ATAGI advice which reiterated that it is highly likely

that zoster vaccine efficacy could wane at a faster rate in those vaccinated at an older age compared with a younger age and the assessment of the duration of vaccine efficacy in other jurisdictions. In this context, the PBAC noted that the ESC's proposal of a 10 year duration is likely to be an overestimate in the resubmission's proposed older cohort of 70 year olds. The PBAC considered that a seven year duration of vaccine efficacy for both prevention of zoster and prevention of PHN may be reasonable given the current evidence, and that this should be used to inform the revised base case to establish cost-effectiveness.

7.9 The PBAC recalled in consideration of the 60+ year cohort in March 2008 that the cost effectiveness of the vaccine in this context should be compared to other population preventative interventions such as lipid-lowering and anti-hypertensive drugs rather than with treatment of patients with severe symptomatic disease such as late stage cancer. In addition, the PBAC noted that the cost effectiveness of the vaccine in this context relied on an improvement in the quality of life rather than on an extension of life.

7.10 The PBAC considered that the financial estimates appeared reasonable, but the projected cost to Government may be lower in light of the ATAGI advice that uptake of the vaccine may be lower than presented in the submission, in line with observed current vaccine uptake in adults.

7.11 Given the uncertainty of the duration of the efficacy of this vaccine against zoster and PHN and the proposed large financial outlay by government, the PBAC agreed with ATAGI that the establishment of an adult vaccination register is high priority. [redacted]

Outcome:
Recommended

8 Recommended listing

8.1 List zoster virus vaccine live on the NIP for immunocompetent persons aged 70 years, and a catch-up cohort of immunocompetent persons aged 71 to 79 years.

9 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.

10 Sponsor's Comment

bioCSL welcomes the PBAC's recommendation for listing zoster virus vaccine live (ZOSTAVAX), addressing the unmet public health need to prevent the burden of zoster and post herpetic neuralgia in older Australians. We look forward to the program commencing as soon as possible. However, bioCSL disagrees with the PBAC's assumption of no vaccine efficacy after seven years, which is inconsistent with the recent publication of the LTPS study (Morrison et al. 2014)[1].

[1] Corrected Proofs available at http://cid.oxfordjournals.org/content/early/2014/12/18/cid.ciu918.full.pdf+html?sid=b9f62971-4908-465d-a94d-71ee764f6a29.