PUBLIC SUMMARY DOCUMENT

Product: ZOSTER VIRUS VACCINE LIVE, 0.65 mL injection, prefilled syringe, Zostavax®
Sponsor: bioCSL (Australia) Pty Ltd
Date of PBAC Consideration: March 2014

1. Purpose of Application

The major re-submission sought to reinstate the PBAC recommendation for the listing of zoster vaccine in the National Immunisation Program (NIP) for 60 year olds and a catch-up cohort of 61-79 year olds.

The PBAC noted that the sponsor in its pre-PBAC response proposed a change to the purpose of the application, to seek the listing of zoster vaccine in the NIP for 70 year olds and a catch-up cohort of 71-79 year olds. This proposal had not been evaluated nor considered by the Economics Subcommittee (ESC) or Australian Technical Advisory Group on Immunisation (ATAGI) for these more restricted cohorts.

The PBAC noted that zoster vaccine was recommended by the Joint Committee on Vaccination and Immunisation (JVCI) for a similar cohort in the UK (70-79 year olds). The PBAC also noted that, in implementing this program, the UK's National Health Service (NHS) provides the vaccine to 70 year olds and 79 year olds, as there were issues for the supply the vaccine for the entire 71-79 year old catch up cohort.

2. Background

This was the fourth time that the PBAC had considered zoster vaccine. The first submission was considered at the November 2007 PBAC meeting. A minor re-submission was considered at the March 2008 PBAC meeting, at which zoster vaccine was recommended for listing in the NIP for 60 year olds and a catch-up cohort of 61-79 year olds. In July 2013, the 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. For the July 2013 PBAC meeting, ATAGI identified key model inputs that may have changed since the 2008 recommendation and may affect the estimation of cost effectiveness. The PBAC considered that:

- estimates of vaccine effectiveness in the new data varied, although they were generally consistent with the SPS study;
- it was not possible to discount the possibility that the duration of immunity is less than was predicted in 2008. The PBAC considered that these long-term follow-up data suggest that a booster dose of zoster vaccine is likely to be needed, which increases uncertainty about the cost-effectiveness of the vaccine;
- the same disutility may not be observed (and therefore avoided by vaccination) in the contemporary setting with newer treatments for PHN available since 2008;
- infant varicella (chickenpox) immunisation may alter the burden of illness of the condition, and thereby altering population size and disease severity.

The PBAC considered that the new data published since its March 2008 recommendation meant that the data supporting that recommendation may no longer be representative of the contemporary cost effectiveness of zoster vaccine. The PBAC therefore recommended that the 2008 recommendation be set aside.

3. Registration Status

As of 10 April 2014, Zostavax is TGA registered for the following indications:

- the prevention of herpes zoster (shingles) in individuals 50 years of age and older;
- the prevention of post herpetic neuralgia (PHN) and for the reduction of acute and chronic zoster-associated pain in individuals 60 years of age and older.

4. Listing Requested and PBAC's View

The re-submission requested listing in the NIP as recommended by the PBAC in March 2008. The pre-PBAC response modified the request to the following cohorts of immunocompetent persons:

- ongoing cohort of 70 rather than 60 year old individuals
- catch-up cohort for individuals aged 71-79 rather than 61-79 years.

The PBAC noted that the original re-submission offered the vaccine at a price per dose slightly lower than that recommended in the March 2008. A further price reduction was proposed in the pre-PBAC response for both the ongoing (70 year old) and catch-up (71-79 year old) cohorts. The PBAC noted that the proposed NIP listing is narrower than the TGA indications.

Listing was sought on a cost-utility basis compared with standard medical management of patients with herpes zoster (HZ) / post-herpetic neuralgia (PHN).

5. Clinical Place for the Proposed Therapy

Zoster vaccine is used to prevent zoster and the complications of zoster. The clinical management of zoster / PHN is no different in persons who have been vaccinated or those who have not. This remains unchanged from the original submission in 2007.

6. Comparator

The re-submission nominated standard medical management of patients with zoster / PHN as the comparator. This comparator had been previously accepted by PBAC. New treatments for zoster pain have become available since the previous submission, however the re-submission considered that they were no more efficacious than treatments that were available at the time of the previous submission.

The PBAC agreed that, as new medications (such as pregabalin) were listed on the PBS on a non-inferior basis to other existing treatments, it was reasonable to argue that new treatments have not changed clinical management.

The PBAC considered that standard medical management, as accepted for the 2008 recommendation, remained the appropriate comparator.

7. Clinical Trials

The re-submission was based on the Shingles Prevention Study (SPS, Protocol 004, n=38,546), the key randomised trial considered for the PBAC recommendation in 2008, and the following extension studies of the SPS:

- Short-Term Persistence Substudy (STPS, Protocol 004 X1, n=14,270) follow up of SPS for 4-7 years post vaccination)
- Long Term Persistence Study (LTPS, Protocol 013, n=6,867) single arm follow up of STPS for 7-12 years post vaccination.

Reporting details of the SPS, STPS and LTPS are shown in the table below.

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)	March 2005
	Publications:	
	Oxman, M. N., Levin, M. J., Johnson, G. R., *et al*. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults	*N Engl J Med* 2005; 352(22): 2271-84
	Oxman, M. N. and Levin, M. J. Vaccination against Herpes Zoster and Postherpetic Neuralgia	*J Infect Dis* 2008; 197 (Suppl 2): S228-36
	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	*J Infect Dis* 2008; 197(6): 825-35
	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	*J Infect Dis* 2009; 200(7): 1068-77
	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	*J Am Geriatr Soc* 2010; 58(9): 1634-41
	Simberkoff, M. S., Arbeit, R. D., Johnson, G. R., *et al.* Safety of herpes zoster vaccine in the shingles prevention study: a randomized trial	*Ann Intern Med* 2010; 152(9): 545-54
	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	*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	June 2008
	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	*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	March 2012

The PBAC noted that Protocols 004 V1, 012, 014, 017, 02 and 029 were presented in the re-submission, but were not used to inform the economic evaluation.

The PBAC noted and welcomed the input from individuals (41), health care professionals (2) and organisations (1) via the consumer comments facility on the PBS website and letters to the PBAC. The comments described the impact on older Australians of shingles or the threat of acquiring shingles, and the current cost burden of the vaccine itself and treatment of shingles.

The sponsor requested a hearing for this item. The sponsor presented new values for incremental cost-effectiveness ratios (ICERs) for the economic analysis.

8. Results of Trials

The estimates of efficacy of the vaccine in reducing zoster incidence and PHN are summarised in the tables below. The PBAC noted that, as the LTPS did not have a comparator arm, the re-submission used historical control methods to estimate the long term vaccine efficacy. Vaccine efficacy in the LTPS was estimated using a modelled placebo incidence rate of zoster and PHN, which was extrapolated from historical rates from the SPS and STPS adjusting for age effects and, in the case of zoster, for calendar effects (referred to as Method III in the re-submission)..

Results of reduction in zoster incidence in the direct randomised trial (Protocol 004) and the two extension studies (Protocol 004 X1 and Protocol 013)

Trial ID	Zoster vaccine n / N zoster incidence per 1000 person years	Placebo n / N zoster incidence per 1000 person years	Absolute difference in zoster incidence per 1000 person years	Vaccine efficacy (95% CI)[c]
Protocol 004 (SPS)	315 / 19,254 5.42[a]	642 / 19,247 11.12[a]	-5.70	51.3% (44.2, 57.6)
Protocol 004 X1 (STPS)	84 / 7,320 8.430[a]	95 / 6,950 13.967[a]	-5.537	39.6% (18.2, 55.5)
Protocol 013 (LTPS)	261 / 6,867 10.337	Method I 13.103	-2.766	21.1% (10.9, 30.4)[b]
		Method II 11.64	-1.303	11.2% (-0.3, 21.6)[b]
		Method III 14.126	-3.789	26.8% (17.4, 35.4)[b]

Method I = zoster incidence calculated from SPS adjusting for age and calendar effect
Method II = zoster incidence calculated from SPS adjusting for age
Method III = zoster incidence calculated from SPS+STPS adjusting for age and calendar effect
[a] Weighted average of the observed incidence rate stratified by age group (60-69 and ≥ 70 years) with Mantel-Haenszel weights associated with the total follow-up time in each age group.
[b] The CI is based on the estimated incidence rate of zoster for the placebo group and the 95 % CI for the incidence rate of zoster for the zoster vaccine group.
[c] Calculated as 1 minus the ratio of the estimated incidence rates of zoster in zoster vaccine and placebo groups. The CI was constructed based on the exact conditional procedure stratified by age group.

Results of reduction in PHN incidence in the direct randomised trial (Protocol 004) and the two extension studies (Protocol 004 X1 and Protocol 013)

Trial ID	Zoster vaccine n / N PHN incidence per 1000 person years	Placebo n / N PHN incidence per 1000 person years	Absolute difference in PHN incidence per 1000 person years	Vaccine efficacy (95% CI)[a]
Protocol 004 (SPS)	27 / 19,254 0.464	80 / 19,247 1.384	-0.92	66.5% (47.5, 79.2)
Protocol 004 X1 (STPS)	7 / 7,320 0.704	12 / 6,950 1.764	-1.06	60.1% (-9.8, 86.7)
Protocol 013 (LTPS)	32 / 6,867 1.267	Method I / II 1.962	-0.695	35.4% (8.8, 55.8)[b]
		Method III 1.892	-0.625	33.0% (5.4, 54.2)[b]

Method I / II = PHN incidence calculated from SPS adjusting for age
Method III = PHN incidence calculated from SPS+STPS adjusting for age
PHN cases were defined as zoster-associated pain ≥3 on the Zoster Brief Pain Inventory persisting or appearing ≥ 90 days following onset of zoster rash.
[a] Calculated as 1 minus the ratio of the estimated incidence rates of PHN in zoster vaccine and placebo groups. The CI was constructed based on the exact conditional procedure stratified by age group.
[b] The CI is constructed based on the estimated incidence rate of PHN for the placebo group and the 95 % CI for the incidence rate of PHN for the zoster vaccine group.

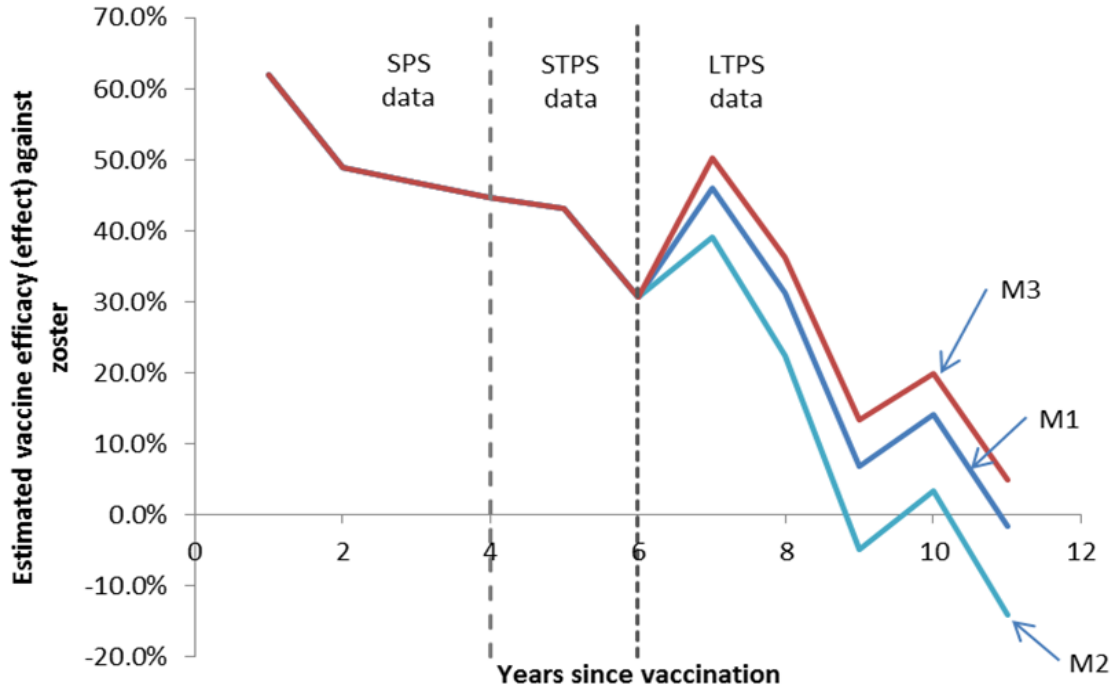
Estimates of comparative benefit from Protocol 004 remained unchanged from the re-submission accepted at the March 2008 PBAC meeting. The PBAC noted that the estimates of benefit from the two extension studies reveal that vaccine efficacy wanes over time.

The PBAC shared the ESC concern about the estimate of the vaccine efficacy from the LTPS. The PBAC noted that the point estimate of vaccine efficacy between year 6 and year 8 increased in relation to the vaccine efficacy of the STPS (year 4-6). The PBAC considered that this increasing vaccine efficacy after vaccination in the modelled data was counter-intuitive and inconsistent with the observed waning efficacy against zoster. The PBAC considered that the vaccine efficacy may be optimistic because there may be a selective drop out of individuals initially recruited in the SPS randomised trial from those subsequently enrolled in STPS and LTPS. Over time, there is likely to be enrichment of the study population of individuals who were successfully vaccinated, as those for whom the vaccine was proven to have failed (i.e. had zoster) or for whom vaccine failure is more likely to occur (i.e. the frail), may be less likely to enrol in follow-on studies.

The PBAC considered that the long term duration of effect was overestimated due to these uncertainties of modelling method. By the end of the LTPS period, the annual rate of zoster cases in the vaccine arm was marginally greater or no greater than the rate of zoster cases in the modelled control arm. The PBAC noted the trial estimates of decreasing vaccine efficacy over time were not used in the economic model, but were used in the discussion presented about proposal of the ongoing cohort of 70 year old individuals.

The PBAC noted that the data indicated that the clinical efficacy, in terms of reduction in zoster in the full SPS/STPS/LTPS trial population , declined to 0% by about year 11-12 post-vaccination (figure below) and, in terms of reduction in PHN in the full SPS/STPS/LTPS trial population , also declined to 0% by about year 11-12 post-vaccination. The PBAC concurred with the ATAGI advice that the results of these studies, overall, provide evidence for waning efficacy of a single dose of zoster vaccine from about year 7-10 post-vaccination.

Point estimates of vaccine efficacy in terms of reduction in the incidence of zoster by years since vaccination



Adverse events remained unchanged from the previous submission. In the period immediately following vaccination, adverse events occurred in 40-50% of patients who were vaccinated (Protocol 014 and Protocol 017). Injection site adverse events were common. Systemic adverse events were not significantly different across the arms in Protocol 014 and Protocol 017. PSURs and two large cohort studies have not reported any specific safety signals of concern. The Vaccine Safety Datalink study did reveal a significant increase in allergic reactions 1-7 days post vaccination.

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

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

Benefits/Harms Summary

	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 III)	6,867	26.8% (17.4, 35.4)	10.34	14.13	-3.8
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 III)	6,867	33.0% (5.4, 54.2)	1.27	1.89	-0.6
	N	**RR (95%CI)**	**Event rate (%)[b]**		**Increment (%)**
			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]	-	-

VSD = Vaccine Safety Datalink
AEMS = adverse event monitoring substudy of Protocol 004 (presented in previous submission)
[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 III 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.
pyr = person years

The PBAC noted that, based on these trials (age at recruitment: 60 years old and over), for every 1000 patients vaccinated with zoster vaccine compared to comparator:

-Up to six patients would avoid herpes zoster per year of follow-up.
-One patient would avoid PHN per year of follow-up.
-320 patients would experience an injection site adverse event.

The committee was not able to estimate benefits or harms for the ongoing cohort of 70 year olds and catch-up cohort of 71-79 year olds.

9. Clinical Claim

The re-submission described the zoster vaccine as being superior in terms of comparative effectiveness and inferior in terms of comparative safety over standard medical management.

The PBAC accepted this clinical claim as being generally supported, but given the issues of selection bias and the modelling approach for the LTPS, the comparative effectiveness was likely to have been overestimated.

The PBAC noted the trial based evidence was not used in the economic analysis in the re-submission. The PBAC considered that, while the modelling in the economic analysis is consistent with a waning effect demonstrated by the clinical data, the time to zero benefit used in the economic model is inconsistent with the duration observed in the extended follow-up studies of the randomized trial. The PBAC considered that it was appropriate to apply the clinical trial evidence to the economic analysis as proposed in the commentary and endorsed by the ESC.

10. Economic Analysis

The re-submission presented a cost utility analysis in the form of a static cohort Markov state transition model, as accepted by the PBAC in 2008. The PBAC considered that the presentation of a cost-utility analysis was appropriate. The PBAC noted that the approach given in the re-submission was identical to that used for the positive recommendation in 2008, but used updated data. A key departure from the previous submission related to the inclusion of an age-specific waning rate of vaccine efficacy in terms of the reductions in the incidence of zoster and PHN.

The results of the economic analysis presented in the re-submission for ongoing (vaccination at 60 years) and catch up cohorts (vaccination 61-79 years) were ICERs in the range of $15,000 to $45,000/QALY for both cohorts.

The PBAC noted that, consistent with the model considered in 2008, the time horizon was for patients up to 105 years of age. This equates to 45 years' duration of modelling for the 60 year old cohort, and is extrapolated from up to 7 years follow up in the pooled results of the SPS and STPS, but did not include the LTPS data. The PBAC noted that this assumption has a high impact on the economic model, favouring the vaccine.

The transition probabilities in model were based on different sources:

- zoster: incidence based on BEACH data, with vaccine arm adjusted for modelled vaccine efficacy from SPS / STPS
- PHN: incidence based on placebo arm of SPS, with vaccine arm adjusted for modelled vaccine efficacy from the SPS / STPS
- dead: all-cause mortality based on ABS data.

The PBAC noted that the ATAGI advice stated the 'HZ disease burden from 2006-2013 BEACH data that has been used in the base case of economic evaluation for 60-79-year olds seems high in comparison to other comparable settings, BEACH and PBS remain the best available sources of data to derive community level HZ incidence estimates although with limitations.' The PBAC noted that incidence of herpes zoster incidence increased between the period of 2000-2006 and 2006-2013 based on the BEACH data and PBS records of anti-viral scripts for herpes zoster treatment.

The PBAC noted that the ATAGI considered that the vaccine efficacy against HZ was overestimated. ATAGI noted that considering a randomised, double-blind, placebo-controlled

trial of zoster vaccine in 50-59 year olds, that the 72.1% vaccine efficacy against HZ modelled in the re-submission for 60 years of age seemed particularly high when compared with range of 69.8-72.4% vaccine efficacy observed in those who were, on average, 5 years younger and thus expected to have a better immune response to zoster vaccine. ATAGI considered the efficacy against PHN at the 60 years of age starting point appears more reasonable.

The PBAC noted that the model of vaccine efficacy was adjusted for waning efficacy, based on a Poisson regression model, rather than clinical trial observations. The regression equation used to model changing vaccine efficacy of PHN was the same as the one generated to predict the incidence of zoster with the age co-efficient removed. The model predicts waning of vaccine efficacy against zoster over 18 years, and against PHN over 37 years among 60 year olds, which is substantially longer than the trial-based duration of protection of 11-12 years. The PBAC agreed with the ESC and considered that the method of back extrapolation for the 60 year old value was inaccurate and would likely over estimate vaccine efficacy.

The PBAC noted that ATAGI considered that the projected duration of vaccine efficacy against HZ and PHN vaccine efficacy in the model appeared implausible and inadequately supported by trial data. The PBAC noted the commentary assumed that efficacy had waned to zero by Year 12 and that there was a zero effect from Year 13 in the modelling. The PBAC agreed with ATAGI and the ESC and considered that vaccine efficacy does not reflect the clinical evidence (SPS, STPS, LTPS) and that it was appropriate to assume on the available evidence that duration of vaccine efficacy against HZ and PHN was 10-12 years.

The PBAC noted that the ESC had commented that, in the utility study used to inform the model, baseline utilities were not collected; rather baseline utility was based on patient recall. The PBAC considered that this may have led to a further overestimation of the gains in quality adjusted life years (QALYs) in the context of both zoster and PHN. 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.

The economic model in the re-submission assumed that:

- the difference in severity and duration of zoster / PHN between the two treatment arms (estimated as a difference in disutilities) in the first 10 years post vaccination was the same as that observed in the first four years post vaccination in the trial data, and
- the difference in severity and duration of PHN between the two arms from 10 years onwards (when the cohort reaches 70 years of age) was the same as those vaccinated at 70+ years of age (40.7%).

This resulted in apparent vaccine efficacy, in terms of a reduction in the severity and duration of PHN, substantially increasing 10 years after vaccination. The PBAC rejected this assumption because it was inconsistent with the observed waning of vaccine efficacy in preventing cases of zoster or PHN.

The reduction in the severity and duration of zoster and PHN (as estimated as a difference in disutilities) attributable to vaccination was assumed to persist over the time horizon of the model (i.e. did not wane). This assumption had a moderate impact on the economic analysis

favouring the zoster vaccine. The PBAC considered this assumption was inconsistent with the observed waning of vaccine efficacy in the trials and it was appropriate that the vaccine efficacy in reducing the severity and duration of zoster / PHN illness lasts no longer than vaccine efficacy against the incidence of zoster / PHN.

The PBAC recalled in recommending zoster vaccine in 2008 that the committee had considered there remained considerable uncertainty about the estimates of QALY gains, given that all benefits are in terms of improvements in morbidity. The PBAC accepted that there are likely to be substantial quality of life (QoL) gains from zoster vaccine (from morbidity avoided).

The PBAC noted that additional analyses were conducted during the evaluation to address some of the key areas of uncertainty. The analyses presented below have been applied to the base-case of the economic model (the 60 year old cohort). The results show that a more conservative estimation of the duration of vaccine efficacy (13 years) in terms of both the reduction in the incidence (1 & 2 below) and severity and duration of zoster (+/- PHN) (4 & 5) substantially increased the ICER from between $15,000-45,000 to between $75,000-105,000.

#	Description of issue	Uncertainty favours	Description of alternative	Alternative ICER (range)
1	Duration of vaccine efficacy against incidence of zoster is inconsistent with that observed in the trials	Intervention arm	Use point estimates of vaccine efficacy against the duration of reduction in the incidence of zoster observed in the SPS / STPS and LTPS Method III. Vaccine efficacy is set to 0 for year 13 onwards.	$15,000-45,000
2	Duration of vaccine efficacy against incidence of PHN is inconsistent with that observed in the trials	Intervention arm	Use point estimates of vaccine efficacy against the duration of reduction in the incidence of PHN observed in the SPS / STPS and LTPS Method III. Vaccine efficacy is set to 0 from year 13 onwards.	$15,000-45,000
3	**Combined effect of: 1 + 2**			$45,000-75,000
4	Model assumes that vaccine efficacy against the burden of illness (measured in differences in disutilities) associated with zoster / PHN improves 10 years post vaccination.	Intervention arm	Assume vaccine efficacy in reducing the burden of illness of zoster / PHN is based on age at vaccination. (eg adjustment of disutilities associated with zoster / PHN in the vaccine arm for 70+ year olds based on vaccine efficacy observed in the 60-69 year old group)	$15,000-45,000
5	Vaccine efficacy against the burden of illness (measured in differences in disutilities) is assumed constant over the time horizon of the model	Intervention arm	Assume vaccine efficacy in reducing the severity and duration of zoster / PHN illness lasts no longer than vaccine efficacy against the incidence of zoster / PHN (this may still be an over-estimate).	$15,000-45,000
6	**Combined effect of 4 + 5**			$15,000-45,000
7	**Combined effect of 3 + 6**			**$75,000-105,000**

The PBAC noted that the ATAGI advice suggested that a 'more plausible base case could be around 10-13 years duration of protection against both HZ and PHN'. The PBAC noted in the ESC Advice that limiting the duration of vaccine efficacy with respect to both zoster and PHN from 13 years to 10 years further increased the ICER to between $75,000-105,000/QALY. The PBAC considered that a significant reduction in the price of the vaccination would be required to achieve the re-submission's base case ICER of $15,000-45,000 /QALY in this re-specified model. The PBAC noted that the ESC considered that the re-specified base case still likely remains an underestimate of the true cost-effectiveness as the analysis did not adjust for the likely reduction in case severity. The PBAC noted that the sponsor was not able to replicate the ICER presented in the ESC Advice, and calculated the ICER to be between $105,000-200,000/QALY.

The PBAC noted that the pre-PBAC response proposed a new price and changed the vaccinee cohorts to an ongoing cohort at 70 years of age and a catch-up cohort 71-79 years of age.

The PBAC noted the ICER/QALY arising from the new proposal was in the range of $15,000-45,000/QALY. The PBAC noted that the sponsor included a disutility assumption where the disutility in vaccinees is equivalent to the disutility in non-vaccinated individuals (0.0131 for zoster and 0.165 for PHN in the 70+ years of age cohort). This assumption, based on the removal of vaccine efficacy as measured as a reduction in the severity and duration of zoster / PHN cases, is more conservative than the assumptions presented in the re-submission.

The PBAC noted that the values of the ICER/QALY presented in the pre-PBAC response were based on the pooled estimates of vaccine efficacy (incidence) from the SPS / STPS / LTPS, where the mean age was 69. The PBAC considered that the vaccine efficacy in the 70+ year old age cohort may not be truly captured in these estimates as the age range in the studies is 60 to 99 years of age. The PBAC noted that incidences of zoster and PHN estimated for the placebo arm (from the SPS) of the LTPS were not separated by age cohort (60-69 and 70+ years) in the re-submission, as was presented for the SPS and STPS. Using vaccine efficacy estimates for only the 70+ year old cohort for years 1-7 (the length of the SPS and STPS), and pooled estimates for years 7-10 (at the price proposed in the pre-PBAC response, with no vaccine efficacy in terms of a reduction in the severity of zoster / PHN), resulted in ICERs of between $15,000-45,000/QALY for the ongoing cohort and for the catch-up cohort.

The PBAC noted that 'ATAGI observed that the rate of waning of vaccine efficacy against HZ for subjects vaccinated at 60 years of age derived from the model appears less steep than what the clinical trial data points suggest. In addition, the pattern and rate of waning against HZ were almost identical when vaccinated at different age points (of 60, 65, 70, 75 and 80 years). ATAGI considered that it was plausible that vaccine efficacy could wane at a faster rate in older individuals, which the model did not account for. Thus, ATAGI considered that there was considerable uncertainty regarding how the re-submission had presented changes in vaccine efficacy by age at vaccination and time since vaccination. The estimates of vaccine efficacy against both HZ and PHN reported for the whole vaccine cohort (mean age at vaccination 69.4 years) by year of follow-up in the SPS, STPS and LTPS were highly variable and imprecise from year 5 onwards for HZ and Year 3 onwards for PHN. These estimates had wide confidence intervals with lower bounds extending to below zero for almost all years from year 6 for HZ and from year 3 for PHN. Higher estimates appeared in

years between the SPS and STPS, when, as discussed in the ATAGI pre-submission advice of October 2013, there were issues with trial participant follow-up. ATAGI questioned whether the use of relatively high point estimates, which are either highly imprecise or statistically non-significant, may have unduly influenced the model to suggest a longer duration of efficacy against both outcomes than would be suggested by the raw data. ATAGI suggested that these uncertainties inherent from the trial data should be modelled using a more conservative approach.'

11. Estimated PBS Usage and Financial Implications

The approach used by the re-submission was identical to that used in the 2007 submission.

Based on the re-submission's original proposal for vaccination of a 60 year old cohort and a catch-up cohort of 61-79 years old, the likely number of patients per year was estimated to be greater than 200, 000. The estimated total net cost per year to the government ranged from > $100 million in years 1 and 2 to $60-100 million in years 3-5.

The PBAC noted that the proposal for the 70 year old cohort, assuming 80% uptake, was estimated to cost between $10 million and $30 million per year ongoing. The catch-up program for a 71-79 year old cohort was estimated to be a one-off cost of greater than $100 million. The PBAC noted that the hearing on the item suggested that the size of the newly proposed cohort would be reduced from the original re-submission's estimate of vaccinees between the age of 60 and 79 years. The assumptions for the derivation of the number of vaccinees greater than 70 years of age were not presented during the evaluation period of this item.

The re-submission proposed a rebate per dose would be offered for vaccines supplied in the first five years of the program to assist with the establishment of a vaccination register for zoster vaccine. The proposed contribution to the vaccination register would be between $10 million and $30 million. The PBAC was uncertain of the status of this rebate with the modification of the proposed listing in the pre-PBAC response.

12. PBAC Outcome

The PBAC deferred making a recommendation in relation to the re-submission to seek the listing of zoster virus vaccine in the National Immunisation Program (NIP) for 70 year olds and a catch-up cohort of 71-79 year olds, as this proposal was presented to the PBAC without sufficient time to evaluate the changes from the re-submission. The PBAC did not recommend the reinstatement of the previous PBAC recommendation for the listing of zoster virus vaccine in the NIP for 60 year olds and a catch-up cohort of 61-79 year olds, because of unacceptable assumptions in the economic analysis such as the inconsistency between estimates of vaccine efficacy between the trial with its follow up studies and the economic model.

The PBAC recalled that, in making the recommendation in July 2013 to set aside the recommendation of March 2008, the committee had considered that:

- estimates of vaccine effectiveness in the new data varied, although they were generally consistent with the SPS study;

- it was not possible to discount the possibility that the duration of immunity is less than was predicted in 2008. The PBAC considered that these long-term follow-up data suggest that a booster dose of zoster vaccine is likely to be needed, which increases uncertainty about the cost-effectiveness of the vaccine;
- the same disutility may not be observed (and therefore avoided by vaccination) in the contemporary setting with newer treatments for PHN available since 2008;
- infant varicella immunisation may alter the burden of illness of the condition, and thereby altering population size and disease severity.

In the context of this resubmission, the PBAC considered that, as new medications (such as pregabalin) were listed on the PBS on a non-inferior basis to other treatments, it was reasonable for the re-submission to argue that new treatments have not changed the clinical management of zoster in the contemporary setting.

The PBAC noted the re-submission did not directly address the concern of the PBAC on effects of infant varicella immunisation in the context of the zoster vaccine. In additional to the information provided in the re-submission, the PBAC noted that ATAGI considered that the evidence to date does not support any substantial changes in the severity of HZ attributable to the childhood varicella vaccination program that needs to be taken into account in the economic analysis of zoster vaccine.

The PBAC recalled that the need for a booster was unclear in its 2008 consideration and that a risk share proposal about the provision of a booster was suggested by the PBAC to mitigate against the uncertain duration of vaccine efficacy. The PBAC noted that the re-submission stated that zoster vaccine is cost-effective in the absence of a booster and any decision regarding a booster would be the subject of a separate submission to PBAC. The PBAC noted that: 'ATAGI does support consideration of the option of revaccination (booster) with zoster virus vaccine later in life for those who receive a first dose at age 60 years. This consideration is based on: (1) evidence of waning immunity against HZ and PHN; (2) life expectancy of Australians at 60 (or 70) years of age that considerably exceeds the duration of protection; and (3) increasing risk of HZ with age.' The PBAC noted that the efficacy of the zoster vaccine following a booster dose has not yet been established.

The PBAC considered that the vaccine efficacy modeled in the economic analysis was inconsistent with the new clinical data by suggesting efficacy for preventing zoster extending to 18 years and 37 years for PHN in the 60 year old cohort. The extended effectiveness studies suggest waning efficacy over 10-12 years.

The PBAC noted that the application of the disutilities in the economic model produced a gain in vaccine efficacy in terms of the burden of illness at 70 years which was inconsistent with the clinical data. The PBAC considered it was inappropriate to apply this assumption in the economic model.

The PBAC considered that the incremental cost-effectiveness of the zoster vaccine was unacceptably high and uncertain ($75,000-105,000 /QALY) when these assumptions were appropriately adjusted to:

- use point estimates of vaccine efficacy against the duration of reduction in the incidence of zoster and PHN observed in the SPS / STPS and LTPS Method III, such that vaccine efficacy is set to 0 from year 10 or 13 onwards

- assume vaccine efficacy in reducing the severity and duration of zoster / PHN illness lasts no longer than vaccine efficacy in reducing the incidence of zoster / PHN
- assume vaccine efficacy in reducing the severity and duration of illness of zoster / PHN is based on age at vaccination (e.g. adjustment of disutilities associated with zoster / PHN in the vaccine arm for 70+ year olds is based on vaccine efficacy observed in 60-69 year olds).
- The PBAC noted that, after adjusting for these issues in the economic model, a significant price reduction would be required to achieve the ICER proposed in the re-submission of $15,000-45,000 /QALY.

The PBAC noted that the late change to the purpose of the application, to seek the listing of zoster vaccine in the NIP for 70 year olds and a catch-up cohort of 71-79 year olds, was not able to be evaluated. The PBAC had four areas of concern.

First, the PBAC noted that, since the first submission for zoster vaccine in mid-2007, the intended cohort for vaccination was individuals at 60 years of age. The pre-PBAC response did not present the clinical rationale for selecting the 70 year old age group rather than the 60 year old age group for the NIP, beyond indicating that a similar program had recently been implemented in the UK.

Second, the PBAC considered that there was clear evidence of a reduced initial vaccine efficacy with increased age. Though the mean age in the clinical trials was 69 years, the PBAC considered that it was inappropriate to apply the vaccine efficacy estimates based on the age range of 60 to 99 years of age (i.e. all ages in the SPS trial and extensions). The PBAC considered that presentation of the clinical trial data in age blocks (for example, 60-64, 65-69, 70-74 and 75-79 years) would allow a clearer consideration of the age-effect on vaccine efficacy. The PBAC recognised the uncertain direction of bias in the LTPS results, given the lack of a placebo arm which would likely not inform decision making. The PBAC noted that ATAGI commented that the estimates of vaccine efficacy against both HZ and PHN reported for the whole vaccine cohort (mean age at vaccination 69.4 years) by year of follow-up in the SPS, STPS and LTPS were highly variable and imprecise from year 5 onwards for HZ and year 3 onwards for PHN. The PBAC considered that presentation of vaccine efficacy by age block would increase the confidence in the inputs applied to the economic model specific to the 70+ year old age group in the context of all age groups in the studies.

Third, the PBAC considered that there was clear evidence of a more rapid waning of vaccine efficacy with increased age, at least partly due to a reduced initial vaccine efficacy. The PBAC noted that ATAGI considered that it was plausible that vaccine efficacy could wane at a faster rate, due to immune senescence, in those vaccinated at an older age compared with a younger age, which the model did not account for and this possibility did not appear to have been the subject of a sensitivity analysis in the re-submission. Thus, ATAGI considered there was considerable uncertainty regarding how the re-submission had presented changes in vaccine efficacy by age at vaccination and time since vaccination. In addition, ATAGI considered that in the model: if vaccination occurs at age 70 years, estimated protection against HZ becomes zero (from 57.4%) within 13 years which is still shorter than the life expectancy of 70-year-old Australians (16.5 years). Taking the second and third areas of concern together, the PBAC was concerned that vaccine efficacy had not been appropriately applied to the pre-PBAC response model for consideration of the 70+ year old cohort proposals.

Fourth, the PBAC noted that the pre-PBAC response claimed that more than 1 million older Australians would be vaccinated at a cost of between $10 million and $30 million per year ongoing with a one off cost of more than $100 million for the catch-up program. Though these estimates are much lower than in the re-submission, the PBAC considered that it was appropriate that that these estimates should be independently assessed.

The PBAC considered that, to recommend listing of zoster virus vaccination in the NIP for 70 year olds and a catch-up cohort of 71-79 year olds, a full evaluation of the evidence and an opportunity to seek the advice of ATAGI was required. The PBAC considered that if the sponsor wished to request listing of the zoster vaccine in a 70 year old cohort rather than a 60 year old cohort, the supporting evidence and modelling should be consistent with the reduced initial vaccine efficacy and shorter time to waning of effect at the increased age of immunisation. The PBAC considered that the same comparator as presented in this re-submission would be appropriate for a submission in the higher age group. The PBAC 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.

The PBAC considered that a major submission to the PBAC was required to determine cost-effectiveness of zoster vaccine in the 70 year old cohort.

Recommendation:
Deferred

13. 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.

14. Sponsor's Comment

bioCSL will work with the PBAC to achieve a timely 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.