PUBLIC SUMMARY DOCUMENT
Product: ZOSTER VIRUS VACCINE LIVE (Oka/Merk), injection, 0.65 mL, Zostavax®
Sponsor: CSL Biotherapies
Date of PBAC Consideration: November 2007

1. Purpose of Application:

The submission sought listing on the National Immunisation Program (NIP) for the vaccination of an ongoing cohort of 60 year-old individuals and for a catch-up cohort of all individuals 61 years and older against herpes zoster virus (shingles).

2. Background:

This vaccine had not previously been considered by the PBAC.

3. Registration status:

Zoster virus vaccine was originally registered in May 2006 as a formulation that must be stored below minus 15° C. A submission to register a formulation, which can be stored between 2° and 8° C was approved by the TGA Peer Review Meeting on 18 May 2007.

Zoster virus vaccine is indicated for the prevention of shingles, for prevention of postherpetic neuralgia (PHN) and for reduction of acute and chronic zoster-associated pain in individuals 60 years of age and older.

Zoster virus vaccine is indicated for the prevention of shingles in individuals 50-59 years of age based on a study demonstrating similar immunogenicity in this age group compared to those 60 years of age and older.

4. Listing Requested and PBAC's View:

National Immunisation Program (NIP)
For immunocompentent persons aged 60 years and over: an ongoing cohort of 60 year old individuals and a catch-up cohort for all individuals 61 yeas and over.

The PBAC agreed that, in the event of a listing recommendation, zoster virus vaccine would be more ideally suited to the NIP than to the PBS.

5. Clinical Place for the Proposed Therapy:

Currently, the symptoms, severity and complications of herpes zoster are managed with anti-viral therapy (if initiated early enough), and various other non-prescription and prescription only medicines. Zoster virus vaccine provides a vaccination option for prevention against herpes zoster and the resulting complications.

6. Comparator:

The submission nominated standard medical management (SMM) as the appropriate comparator. This was accepted by the PBAC.

7. Clinical Trials

The submission presented the results of a key trial, P004 (Shingles Prevention Study (SPS))– a direct randomised comparative trial comparing one ~20,000-60,000 plaque-forming units (PFU)/0.5mL subcutaneous injection of live attenuated zoster virus vaccine (frozen formulation) plus SMM with placebo injection plus SMM in adults ≥60 years of age with a history of varicella, but without prior episodes of shingles. The median

follow-up was 3.4 years (range 1 day-5.4 years).

The results of a bridging study, P010, were presented in the submission to support the equivalence of the vaccine proposed for the NIP compared with the vaccine used in the clinical studies. Study P010 was a direct randomised comparative trial comparing the refrigerated formulation of live attenuated zoster virus vaccine with the frozen formulation, in adults ≥50 years of age with a history of varicella, with a 28 day follow-up post-vaccination.

The results of a supporting trial, P011, were also presented. Trial P011 was a direct randomised comparative trial comparing one concomitant subcutaneous injection of live attenuated zoster virus vaccine (frozen formulation) with 0.5mL intramuscular injection of inactivated influenza virus vaccine, and one non-concomitant subcutaneous injection of live attenuated zoster virus vaccine (frozen formulation) with 0.5mL intramuscular injection of inactivated influenza virus vaccine in adults ≥50 years of age, with a 28 day follow-up post-vaccination.

The trials have been published as follows:

Trial/First author	Protocol title	Publication citation
P004 Oxman M et al 2005	A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults	NEJM 2005; 352:2271-84
P010 Gilderman Let al 2008	A double-blind, randomized, controlled, multicenter safety and immunogenicity study of a refrigerator-stable formulation of Zostavax	Clin.Vaccine Immunol 2008; 15:2 314-319
P011 Kerzner B et al 2007	Safety and immunogenicity profile of the concomitant administration of Zostavax and inactivated vaccine in adults aged 50 and older	J Am Geriatr.Soc 2007; 55:10 1499-1507

8. Results of Trials

The results of the key trial are summarised below.

Key trial (P004): Results for the incidence of herpes zoster and post-herpetic neuralgia (PHN)[a]

Group	Zoster vaccine (N=19,270) Frozen, ~20,000-60,000 PFU/0.5mL		Placebo (N=19,276)		
Incidence of herpes zoster	**cases/ total**	**Incidence per 1,000 patient yrs**	**cases/ total**	**Incidence per 1,000 patient yrs**	**RRR % (95% CI)**
60-69 years	122/10,370	3.90	334/10,356	10.79	63.9 (55.5, 70.9)
≥70 years	193/8,884	7.18	308/8,891	11.50	37.6 (25.0, 48.1)
MITT	315/19,254	5.42	642/19,247	11.12	51.3 (44.2, 57.6)
ITT	321/19,270	5.37	660/19,276	11.13	51.7 (44.7, 57.9)
Male	181/11,390	5.29	361/11,337	10.65	50.2 (40.4, 58.6)
Female	134/7,864	5.58	281/7,910	11.78	52.7 (41.6, 61.7)
Incidence of PHN					
60-69 years	8/10,370	0.27	23/10,356	0.75	65.7 (20.4, 86.7)
≥70 years	19/8,884	0.72	57/8,891	2.14	66.8 (43.4, 81.3)
Male	19/11,390	0.57	51/11,337	1.51	62.8 (35.9, 79.3)
Female	8/7,864	0.34	29/7,910	1.23	72.6 (38.6, 89.2)
MITT	27/19,254	0.46	80/19,247	1.38	66.5 (47.5, 79.2)
ITT	28/19,270	0.47[d]	80/19,276	1.35[d]	65.2 (45.9, 89.2)

[a] PHN defined as zoster-associated pain ≥3 persisting or appearing ≥90 days after the zoster rash onset. 0 = pain free. 0-10 scale where 0 = no pain and 10 = pain as bad as you can imagine; MITT = modified intention to treat population i.e. all subjects who were followed for ≥30 days post-vaccination and did not develop evaluative herpes zoster within 30 days post-vaccination; RRR = relative risk reduction; yrs = years

The population of most relevance in the context of NIP listing application is the Modified-Intent-To-Treat (MITT) population. The MITT population included all subjects who were followed for ≥ 30 days post-vaccination and did not develop evaluable herpes zoster within 30 days post-vaccination. There was a statistically significant reduction in the co-primary outcome, incidence of PHN, for the zoster virus vaccine (plus SMM) group versus the placebo (plus SMM) group in the MITT population (p-value <0.001). There was a statistically significant reduction in the secondary outcome, incidence of herpes zoster, for the zoster virus vaccine (plus SMM) group versus the placebo (plus SMM group) in the MITT population (p-value < 0.001 for testing the vaccine efficacy for herpes zoster > 25%).

Vaccine efficacy for the prevention of herpes zoster appeared to be inversely correlated with age at vaccination. The vaccine was more effective at preventing herpes zoster in the 60-69 age group (approximately 7 cases/1,000 person years prevented) than in the ≥70 age group (approximately 4 cases/ 1,000 person years prevented). Between the ages of 60-69 years there was a reduction in risk of herpes zoster of 63.9%, whereas by 70 years and older the reduction in risk had decreased to 37.6%. This may have implications for the value of a catch-up program in this age group, as well as the potential requirement for a booster dose after 10 years in the 60 year old cohort. However, the reduction in the risk of PHN, defined as the persistence of clinically significant zoster pain for ≥ 3 months, was not age dependent. Between the ages of 60-69 years there was a reduction in risk of PHN of 65.7% and a similar reduction in risk of PHN of 66.8% was observed in subjects aged 70 years and older.

The results for the other co-primary outcome, the zoster burden of illness (ZBOI) in each treatment group in trial P004, are summarised in the table below.

Trial P004 - results for zoster burden of illness (ZBOI)[a], co-primary outcome

ZBOI	zoster cases/ total	BOI score	zoster cases/ total	BOI score	RRR % (95% CI)
60-69 years	122/10,370	1.50	334/10,356	4.33	65.5 (51.5, 75.5)
≥70 years	193/8,884	3.47	308/8,891	7.78	55.4 (39.9, 66.9)
Male	181/11,390	2.09	361/11,337	5.81	64.0 (51.4, 73.4)
Female	134/7,864	2.34	281/7,910	5.47	57.3 (39.6, 69.8)
MITT	315/19,254	2.21	642/19,247	5.68	61.1 (51.1, 69.1)
ITT	321/19,270	2.29	660/19,276	5.79	60.4 (50.2, 68.6)

[a] ZBOI is a composite endpoint incorporating the incidence of herpes zoster, and severity and duration of zoster pain; RRR = relative risk reduction

There was a statistically significant reduction in ZBOI for the zoster virus vaccine group (plus SMM) versus the placebo (plus SMM) group in the modified intention to treat (MITT) population (p-value <0.001). However, the interpretation of ZBOI is difficult because it was a composite score.

Trial P004 - duration of zoster pain among evaluative zoster cases in the MITT population

Group	Endpoint	Zoster virus vaccine (N=19,270) Frozen, ~20,000-60,000 PFU/0.5mL		Placebo (N=19,276)	
		cases	median duration, days (95% CI)	cases	median duration, days (95% CI)
All subjects	Duration of clinically significant zoster pain	313	20 (16, 23)	638	22 (21, 25)
	Duration of any zoster pain	313	36 (30, 44)	638	38 (35, 42)
60-69 years	Duration of clinically significant zoster pain	121	17 (13, 23)	332	20 (16, 22)
	Duration of any zoster pain	121	30 (26, 36)	332	36 (32, 41)
≥70 years	Duration of clinically significant zoster pain	192	21 (16, 27)	306	27 (22, 31)
	Duration of any zoster pain	192	41 (33, 47)	306	41 (36, 49)

There was a statistically significant and clinically important reduction in the median duration of clinically significant zoster pain for the zoster virus vaccine (plus SMM) group versus the placebo (plus SMM) group (log-rank p-value <0.001 and 0.041 in the MITT population and among all evaluative zoster cases respectively).

Trial P004 - general health state reported on the EuroQoL VAS among evaluative zoster cases in the MITT population

Time point (relative to zoster rash onset)	Zoster virus vaccine Frozen, ~20,000-60,000 PFU/0.5mL (N=19,270)		Placebo (N=19,276)	
	n	Observed mean score (95% CI)	n	Observed mean score (95% CI)
Week 1	247	73.9 (71.5, 76.2)	519	73.0 (71.3, 74.7)
Week 12	276	83.2 (81.4, 84.9)	575	81.9 (80.5, 83.3)
Week 26	279	84.5 (82.7, 86.3)	580	83.0 (81.6, 84.5)

EuroQoL = 100 point scale where 0 represents the worst imaginable health state and 100 represents the best imaginable health state; n = number of evaluative zoster patients who reported EuroQoL information at the respective visit

There was no statistically significant difference in the incidence of substantial activities of daily living interference (ADLI) experienced by patients who developed herpes zoster in the zoster virus vaccine (plus SMM) group versus the placebo (plus SMM) group (p-value = 0.341 for testing the vaccine efficacy for substantial ADLI beyond zoster >0%). Quality of life scores measured in the first 6 months after onset of herpes zoster using the SF-12 health survey and EuroQoL visual analogue scales were similar for both treatment groups.

With respect to the bridging study, P010, the pre-specified non-inferiority criterion in the primary analysis was met.

In the supporting trial, P011, the pre-specified non-inferiority criterion in the primary analysis was met, suggesting that zoster virus vaccine (frozen formulation) administered concomitantly with inactivated influenza virus vaccine is non-inferior to these vaccines administered non-concomitantly.

The PBAC had a number of clinical concerns, see Recommendation and Reasons.

Comparative toxicity

In the key trial, P004, one or more adverse events (AEs) were reported by 58.1% and 34.4% patients in the zoster virus vaccine (plus SMM) group versus the placebo (plus SMM) group respectively in the adverse event monitoring sub-study of trial P004. There was a higher proportion of patients that experienced injection-site adverse events (95% CI 29.6%, 33.8%) and vaccine related adverse events (95% CI 28.3%, 32.6%) in the zoster virus vaccine (plus SMM) group versus the placebo (plus SMM) group. Most of the injection-site adverse events were reported as mild and of brief duration.

The only systemic clinical AEs reported with an incidence ≥2% in one or more treatment groups were headache, respiratory infection, and rash. Of these, there was a slightly higher incidence of vaccine-related headache in the zoster virus vaccine (plus SMM) group versus the placebo (plus SMM) group (1.4% versus 0.9%, respectively; 95% CI 0.0, 1.1).

In the bridging study, P010, 45.8% and 55.0% of patients reported one or more clinical adverse experiences in the refrigerated vaccine group versus the frozen vaccine group respectively. The most commonly reported systemic AE in each treatment group was headache (3.3%). There was a slightly higher incidence of musculoskeletal and connective tissue disorders in the refrigerated vaccine group compared to the frozen vaccine group (5.6% versus 1.6% respectively; 95% CI 0.1, 8.5).

In the supporting trial, P011, AEs were similar between the vaccination groups, although there was a trend toward a higher incidence of AEs in the concomitant vaccines group. 1.6% subjects in the concomitant group and 1.3% in the non-concomitant group reported serious AEs. The most commonly reported systemic AE in either treatment group was upper respiratory infection (5.0% and 4.5% in the concomitant and non-concomitant groups respectively).

9. Clinical Claim

The submission claimed that Zostavax is therapeutically superior and has significant clinical advantages over standard medical management but has greater toxicity.

See Recommendation and Reasons for the PBAC's view of this claim.

10. Economic Analysis

A modelled economic evaluation was presented. The choice of the cost-utility approach was considered valid. The resources included were drug costs, costs of principal and non-principal hospitalisations, emergency department visits, GP visits, specialist referrals, and vaccination costs.

The submission calculated the base case modelled incremental discounted cost/extra discounted quality adjusted life year (QALY) to be in the range of $15,000 - $45,000 for a cohort of 60-year olds.

The incremental cost/QALY for the catch up cohort increased with increasing age, falling into the range $15,000 - $45,000 for 65, 70 and 75 year olds, $45,000 – 75,000 for 80 and

85 years olds, and $75,000 - $200,000 for persons aged 90 or above.

The PBAC considered the accuracy of these results was highly uncertain given problems identified with the model, *see Recommendation and Reasons.*

11. Estimated PBS Usage and Financial Implications:

The submission estimated that the number of vaccination doses given per year to be greater than 200,000 doses. The submission also estimated that once the vaccination program for 60 year-olds reaches steady state the cost will be in the approximate range of $20 - $40 million per year and the total cost for the catch up program to be approximately greater than $100 million.

12. Recommendation and Reasons

The PBAC agreed that placebo together with standard medical management (SMM) was the appropriate comparator. The PBAC further agreed that, should listing on the NIP be recommended at some future time, it should not exclude patients who had already experienced an episode of herpes zoster (i.e. the vaccine should be allowed for both primary and secondary prevention of zoster).

The PBAC also agreed that herpes zoster is a significant public health issue, particularly for the elderly, and that the data presented from the key Shingles Prevention Study (SPS, 004) are supportive of the effectiveness of vaccination in reducing the incidence of herpes zoster and postherpetic neuralgia (PHN) in the primary cohort of 60 year olds proposed to be immunised through the NIP. However the PBAC considered that there were a number of problems with the submission as follows:

Firstly, the Committee noted that the vaccine proposed for inclusion on the NIP is not the same as the vaccine used in the key clinical trial and furthermore that no data from an appropriate bridging study are available. The key SPS clinical trial used a frozen vaccine containing approximately 20,000-60,000 (median 24,000) plaque-forming units (PFU)/0.5mL live attenuated varicella-zoster virus (VZV). The bridging study presented in the submission (P010) compared a frozen vaccine containing 56,845 PFU/0.65mL with a refrigerated vaccine containing 44,846 PFU/0.65mL. The refrigerated vaccine proposed for the NIP contains a minimum of 19,400 PFU/0.65mL at expiry.

Data to demonstrate that the immune response to the vaccine increases linearly with increasing PFU is not presented. Furthermore, a threshold effect where doses below the threshold do not provide immunity cannot be excluded. Such a threshold effect has been seen with other vaccines including live attenuated vaccines such as the varicella vaccine. Thus, there is clinical uncertainty in relation to potential differences in the effectiveness of the vaccine proposed for the NIP compared with the vaccine used in the clinical studies. The PBAC considered it appropriate for further bridging data to be provided in support of any future application for inclusion of this vaccine on the NIP.

A second area of clinical concern for the Committee was the limited evidence for safety and efficacy of zoster virus vaccine in older adults, given the low number of patients aged over 80 years in the trial. This is particularly relevant for the proposed catch-up program.

A third area of clinical concern is the lack of data to demonstrate that co-administration of the zoster vaccine with the pneumococcal, polysaccharide vaccine (PPV23) is non-inferior to the two vaccines administered non-concomitantly. The PBAC noted that concomitant administration of the two vaccines was likely to occur in clinical practice and that, although the submission has provided data in support of the concomitant administration of the zoster vaccine and the influenza virus vaccine, no such data are provided in respect of the pneumococcal vaccine.

A fourth issue of concern for the Committee was the uncertainty in the submission's estimated base-case incremental discounted cost per extra discounted quality adjusted life year (QALY) gained, especially in the context of a preventative health measure. This uncertainty arises from a number of sources including doubts about the validity of the claimed life-long assumption of efficacy and doubts about the generation of utility weights and the derivation of the QALY loss associated with herpes zoster.

With respect to the duration of vaccine efficacy, the median follow up data presented for the SPS study was 3.4 years (range 1 day – 5.4 years). However, the base case results of the economic evaluation are based on the assumption of lifelong protection against herpes zoster. The submission argued that if vaccine efficacy is assumed to last for 12 years, the incremental cost-effectiveness ratio is in the range of $45,000 - $75,000. The PBAC considered this to be unacceptably high in the context of the proposed vaccine as a preventative health measure. The PBAC considered that the uncertainty associated with the duration of effect could be appropriately addressed through a risk-sharing arrangement whereby free vaccine is provided if a booster dose is required within an appropriate time period for this disease.

The PBAC also considered that the submission's approach to calculating disutilities is problematic and if the true disutility values were lower, the ICER would increase.

The PBAC noted that the base case in the economic model assumes both a reduction in the incidence of zoster cases and an improvement in the quality of life compared to no vaccination in those instances where a zoster cases occurs. On the other hand, the evidence provided by the 004 trial is for a reduction in incidence and for a reduction in the median duration of clinically significant zoster pain with the vaccine which was not translated into a difference in the quality of life of patients who developed zoster as measured by the EuroQoL VAS instrument.

The PBAC further noted that in spite of a much greater absolute reduction in the risk of PHN in the over 70 year old group in the 004 trial, this did not appear to translate into a quality of life benefit as might be expected. This added to the Committee's uncertainty about the effect of immunisation on quality of life.

The fifth issue of concern for the PBAC was the increase in the estimated ICERs with increasing age. The Committee considered that the uncertainty about the different efficacy and hence cost-effectiveness of the vaccine in various populations would usually be addressed through a risk-sharing arrangement whereby the price is adjusted to maintain cost-effectiveness.

Finally, the PBAC further agreed with other clinical and economic concerns raised during the evaluation, with the exception that the PBAC agreed with the submission regarding the derivation of hospitalisation and emergency department costs.

Therefore, the PBAC rejected the application on the basis of uncertain cost-effectiveness against the comparator, placebo, noting the following:

- there is clinical uncertainty in relation to (1) potential differences in the effectiveness of the vaccine proposed for the NIP compared with the vaccine used in the clinical studies; (2) the efficacy of the vaccine in people aged over 80 years and (3) the concomitant administration of the zoster and pneumococcal vaccines;
- there is a high level of uncertainty in the incremental cost effectiveness ratio, especially in the context of a preventative health measure; and
- there are large increases in the incremental cost-effectiveness ratio with increasing age in the catch-up population

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

CSL is disappointed with the PBAC decision to reject the application for NIP funding, noting with concern the requirement for preventative health measures to meet even more onerous cost-effectiveness thresholds than interventional treatments. This is exacerbated by application of the 5% discount rate which particularly disadvantages vaccination programs, with single up-front costs, as compared to ongoing pharmaceuticals.

CSL contends that multivariate sensitivity analyses presented in the submission support the robustness of the modelled economic evaluation, noting that incremental cost-effectiveness ratios were in the range of $15,000 - $45,000/QALY for more than 80% of scenarios tested.

CSL has presented a re-submission for consideration at the March 2008 meeting of the PBAC and hopes to achieve a favourable outcome that will reduce the significant public health burden of herpes zoster and its complications in the Australian population.