PUBLIC SUMMARY DOCUMENT
Product: Zoster Virus Vaccine Live (Oka/Merk), injection, 0.65 mL, Zostavax®
Sponsor: CSL Biotherapies
Date of PBAC Consideration: March 2008

1. Purpose of Application

The submission sought a 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

At the November 2007 meeting, the PBAC rejected the application for zoster virus vaccine 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.

3. Registration Status

Zoster virus vaccine was originally registered by the TGA on 11 May 2006 as a formulation that must be stored below minus 15° C. A formulation which can be stored between 2° and 8° C was registered on 19 June 2007.

Zoster virus vaccine is indicated for the prevention of herpes zoster (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 herpes zoster (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

For the prevention of herpes zoster (shingles), for prevention of postherpetic neuralgia and for reduction of acute and chronic zoster-associated pain for immunocompetent persons aged 60 years and over: an ongoing cohort of 60 year old individuals, and a catch-up cohort for all individuals 61 years and over.

See Recommendation and Reasons for PBAC's view.

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 as the appropriate comparator. This was accepted by the PBAC.

7. Clinical Trials

The submission presented data from an early pilot study (Protocol 001) and from the Shingles Prevention Study (SPS) (Protocol 004) Clinical Study Report.

8. Results of Trials

New data from Protocol 001 and from Protocol 004 suggested that 19,000 plaque forming units (PFUs)/dose represented a minimum threshold for eliciting a cell mediated immune response, and there was no additional response with doses greater than this. That is, doses greater than 19,000 PFU/dose are above a no-effect threshold. The maximum release potency for refrigerated Zostavax was set at 202,800 PFU/0.65 mL dose and the minimum release potency was set at 44,525 PFU/ 0.65 mL dose. This release potency ensures Zostavax has greater than 19,400 PFU/dose at shelf life expiry.

7% of participants in the SPS (Protocol 004) were 80 years and older. No additional safety or efficacy data were presented for persons over the age of 80 years.

The PBAC were advised that no additional clinical studies were being conducted specifically in older adults. However, ongoing regulatory and pharmacovigilance studies will provide post marketing data in all age cohorts.

9. Clinical Claim

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

10. Economic Analysis

The submission presented an updated modelled economic evaluation with the primary difference being a new price offered. For the vaccination ages of 60 and between 61-79, the incremental cost-effectiveness ratios (ICER) per Quality-Adjusted Life-Year (QALY) was between $15,000 and $45,000. For the vaccination age range between 80-100, the ICER per QALY was between $45,000 and $75,000.

The submission also presented the incremental cost-effectiveness of Zostavax should a booster dose be needed between 6 and 25 years after the initial vaccination course. The ICER per QALY was between $15,000 and $45,000 for each booster stage (6, 12, 18 and 25 years).

Additional sensitivity analyses were performed on disutilities associated with zoster and PHN which were of concern at the November 2007 PBAC meeting. The results of the analyses are shown in the table below.

Variable (reference for sensitivity analysis)	ICER ($/QALY)
Base case	$15,000-$45,000
Disutility for zoster no pain	
4 weeks	$15,000-$45,000
0 weeks	$15,000-$45,000
Additional analyses	
Average pre-zoster score	$15,000-$45,000
Disutility vaccinated = non vaccinated	$15,000-$45,000

11. Estimated PBS Usage and Financial Implications

For the 60 year-old cohort, the estimated number of persons vaccinated was greater than 200,000 in Year 5 at a financial cost to the Government of between $10-30 million in Year 5.

The submission estimated the number of persons vaccinated in the 61-79 year-old catch-up cohort to be considerably greater than 200,000, with a cost to the Government of greater than $100 million in the first 5 years of listing.

The submission estimated the number of persons vaccinated in the 80 year and older catch-up cohort to be greater than 200,000, with a cost to the Government of between $30-60 million in the first 5 years of listing.

12. Recommendation and Reasons

The PBAC recommended listing Zoster Virus Vaccine Live on the National Immunisation Program (NIP) for the vaccination of immunocompetent persons aged 60 years and over (for an ongoing cohort of 60 year old individuals) and a catch-up cohort for all individuals aged between 61 years and less than 80 years on the basis of acceptable cost-effectiveness ratios compared to standard medical management.

The PBAC considered the vaccine should not be made available to persons 80 years and over on the basis of an unacceptably high and uncertain cost effectiveness ratio. In addition, no safety or efficacy data was presented for persons over the age of 80 years. As previously, the PBAC noted 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.

The PBAC noted the minor re-submission addressed key areas of uncertainty raised by the PBAC at its November 2007 meeting.

The PBAC considered the new data provided reassurance with respect to the comparability of the frozen and refrigerated formulations of Zostavax. The submission presented data from an early pilot study (Protocol 001) and from the Shingles Prevention Study (SPS) (Protocol 004) Clinical Study Report suggesting that 19,000 plaque forming units (PFUs)/dose represented a minimum threshold for eliciting a cell mediated immune response and there was no additional response with doses greater than this, i.e. doses greater than 19,000 PFU/dose are above a no-effect threshold. The maximum release potency for refrigerated Zostavax is set at

202,800 PFU/0.65 mL dose and the minimum release potency is set at 44,525 PFU/ 0.65 mL dose. This release potency ensures Zostavax has greater than 19,400 PFU/dose at shelf life expiry.

The submission advised a study examining the concomitant use of Zostavax and pneumococcal vaccine to look for potential interactions was underway, however, until this issue is resolved, the sponsor undertook to include a statement in all advertising and promotional material that concomitant administration was inappropriate.

With respect to safety and efficacy of zoster virus vaccine in older adults, the PBAC was advised no additional clinical studies are being conducted specifically in older adults, however ongoing regulatory and pharmacovigilance studies will provide post marketing data in all age cohorts.

The uncertainty around the cost-effectiveness ratio in the younger patient cohorts had been addressed by lowering the price of Zostavax such that in the 60 year old cohort and the 61 to 79 year old cohort, the ICERs per extra QALY gained were between $15,000 to $45,000. While the cost of vaccine in the 80 plus age group was also reduced, the ICER per extra QALY gained was unacceptably high at between $45,000 to $75,000.

The PBAC noted additional sensitivity analyses on disutilities associated with zoster and post-herpetic neuralgia gave a range of ICERs per extra QALY gained of between $15,000 and $45,000 in the 60 year old cohort. Nevertheless, the PBAC considered there remains 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 gains from zoster vaccine (from morbidity avoided). It was also noted that listing of the vaccine would not provide a degree of herd immunity as had been the case with rotavirus human papilloma virus vaccines.

Recommendation
ZOSTER VIRUS VACCINE LIVE (Oka/Merk), injection, 0.65 mL

Restriction:	National Immunisation Program For the prevention of herpes zoster (shingles), for prevention of postherpetic neuralgia and for reduction of acute and chronic zoster-associated pain for immunocompetent persons aged 60 years and a catch-up cohort of all individuals aged 61 to 79 years.
Pack size:	1

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 welcomes the PBAC decision to recommend Zostavax for inclusion in the National Immunisation Program following a second submission.

CSL notes that the draft updated zoster chapter in the 9th edition of the Australian Immunisation Handbook, recently circulated for public comment, states that Zostavax vaccine may be administered concurrently with pneumococcal polysaccharide vaccine, 23-valent (23vPPV).