ACE Prevention Briefing Paper No. 6 for March 2008 Steering Committee Meeting

ACE Prevention Briefing Paper: Herpes zoster vaccine

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The following presents interim findings of an assessment of the cost-effectiveness of a vaccine used to prevent herpes zoster (shingles). The assessment is not yet complete (e.g., sensitivity analyses have not yet been completed and the values of variables in the base case have not all been confirmed) therefore results presented below may be subject to change.

1.1 Definition of intervention/s

In 2007, Australia's Therapeutic Goods Administration (TGA) approved the registration of ZOSTAVAX, a vaccine comprising a lyophilized preparation of live, attenuated varicella-zoster virus. According to the product information the vaccine should be administered in a single dose sub-cutaneously.

Herpes zoster, commonly known as shingles, is a manifestation of the reactivation of varicella zoster virus, which, as a primary infection, produces chickenpox (varicella). Anyone who has been infected with varicella zoster virus, including those without a clinical history of varicella, is at risk of developing shingles. Burgess and Gilbert (2003) report that the sera of 97% of Australians aged ≥30 years are positive for varicella antibodies.

1.2 Health states/risk factors affected by the intervention

According to the approved product information, the vaccine is indicated in the prevention of herpes zoster (shingles) and the prevention of associated post-herpetic neuralgia in individuals 50 years of age and older.

1.3 Current Practice

Current practice is to do nothing as there are currently no other interventions that can be used to prevent herpes zoster.

1.4 Efficacy/Effectiveness of intervention/s

A search of the Medline, Embase, and Cochrane Library databases identified a single published report providing results of a relevant trial. In the Shingles Prevention Study (SPS) adults aged ≥60 years were randomised to receive either ZOSTAVAX or placebo (Oxman et al, 2005). The mean duration of follow-up of patients was 3.12 years. Over this time, the overall incidence of herpes zoster per 1000 person- years was significantly reduced by the zoster vaccine, from 11.12 per 1000 person-years in the placebo group to 5.42 per 1000 person-years in the vaccine group ($p<0.001$). The overall incidence of post-herpetic neuralgia was also significantly reduced by the zoster vaccine, from 1.38 cases per 1000 person-years in the placebo group to 0.46 cases per 1000 person-years in the vaccine group ($p<0.001$).

In an integrated analysis of two other clinical trials evaluating immune response to ZOSTAVAX at 4 weeks post-vaccination, responses were generally similar in subjects aged 50 to 59 (N=389) compared to subjects ≥ 60 years of age (N=731) (GMT of 668 vs. 614 gpELISA units/mL, respectively). The geometric mean fold-rise of immune response following vaccination as measured by gpELISA was 2.6-fold (95% CI:[2.4 to 2.9]) in subjects 50 to 59 years of age and 2.3-fold (95%CI:[2.1 to 2.4]) in subjects ≥ 60 years of age. On this basis, it is assumed that results from the SPS are applicable to subjects aged 50-59 years.

1.5 Modelling to health outcomes

Modelling has been used to: (i) apply the evidence from the SPS to the Australian context, (ii) extrapolate outcomes beyond the time horizon of the trial (from 3 years to 10 years and to 50 years); (iii) transform outcomes assessed in the trials (rates of patients with herpes zoster and post-herpetic neuralgia) to a metric that permits comparison of this preventive intervention with other interventions being examined in the ACE Prevention project (i.e., to disability-adjusted survival); and (iv) incorporate provision of resources that are used manage herpes zoster and post-herpetic neuralgia that was not assessed by the trial.

The economic evaluation assessing the cost-effectiveness of the herpes zoster vaccine is conducted using a Markov model. One arm of the model reflects the management algorithm that applies in the scenario where the herpes zoster vaccine is included in the National Immunisation Program (NIP) and the other arm of the model reflects the management algorithm that currently applies (where the herpes zoster vaccine is not included on the NIP).

The structure of the model is illustrated in Attachment 1. Two basic health states are possible in the model:

1. Alive
2. Dead.

All subjects enter the model in the alive state and are free of herpes zoster and post-herpetic neuralgia. Subjects progress through the model in annual cycles. In each cycle of the Markov model:

- a proportion of subjects who are alive (and do not currently have PHN) develop herpes zoster (and the remainder do not). Of those developing herpes zoster:
  - a proportion (28.9%, consistent with the proportion observed in the SPS) develop post-herpetic neuralgia (defined in the model as ongoing pain associated with herpes zoster that was rated as 3 or more on a scale ranging from 0 [“no pain”] to 10 [“pain as bad as you can imagine”] that persists one or more months after the onset of herpes zoster rash) and the remainder do not;
  - of those who have post-herpetic neuralgia in any month, a proportion (60%, consistent with the proportion observed in the SPS) of these experience post-herpetic neuralgia that persists to the following month. In other words, 40% of cases of post-herpetic neuralgia are assumed to resolve in each month. By the end of the year all patients are assumed to have had resolution of post-herpetic neuralgia.

    Herpes zoster and post-herpetic neuralgia are thus assumed in the model to be transient states that are resolved within the annual cycle in which they occur.

- all subjects who commence the cycle in the alive state are assumed to be at risk of death (from any cause in accordance with age- and sex-specific life tables). Those who do not die are then cycled back to the alive state (where they are at risk of herpes zoster and post-herpetic neuralgia). Those who die transit to the dead state. Herpes zoster and post-herpetic neuralgia are assumed to have no impact on rates of mortality.

Monte Carlo simulation (50,000 simulations) is used to generate the results of the economic evaluation. In each simulation, a single person of a specific sex and of a specific starting age is sampled from a distribution representative of Australians aged 50 years or more in 2003. This effectively equates to cost-effectiveness in a catch-up cohort. An additional analysis

examining cost-effectiveness only in individuals that would become eligible for the vaccine once the catch-up cohort has been treated (i.e., for persons aged 50 years) is also presented.

1.6 Costs of interventions and offsets

The cost of the vaccine is assumed to be $150 per dose, which is approximately consistent with cost assumed in an analysis of the cost-effectiveness of the vaccine in the USA as reported by Pellisier et al, 2007. Pellisier is an employee of Merck Research Laboratories, who manufacture the vaccine in the USA. It is assumed that people will be vaccinated at the time they are seeing their GP for other reasons (e.g., when getting vaccinated against influenza), therefore it is assumed that no incremental costs for the administration of the vaccine are applicable. The sensitivity of results to changes in this assumption will be examined.

Cost offsets included in the analysis are costs of managing herpes zoster with a course of anti-viral medication and the costs of hospitalisation for complications associated with herpes zoster. The likelihood of the use of these resources were estimated using the literature, as described in the second bulleted point after Figure 1 in Section 1.7 below.

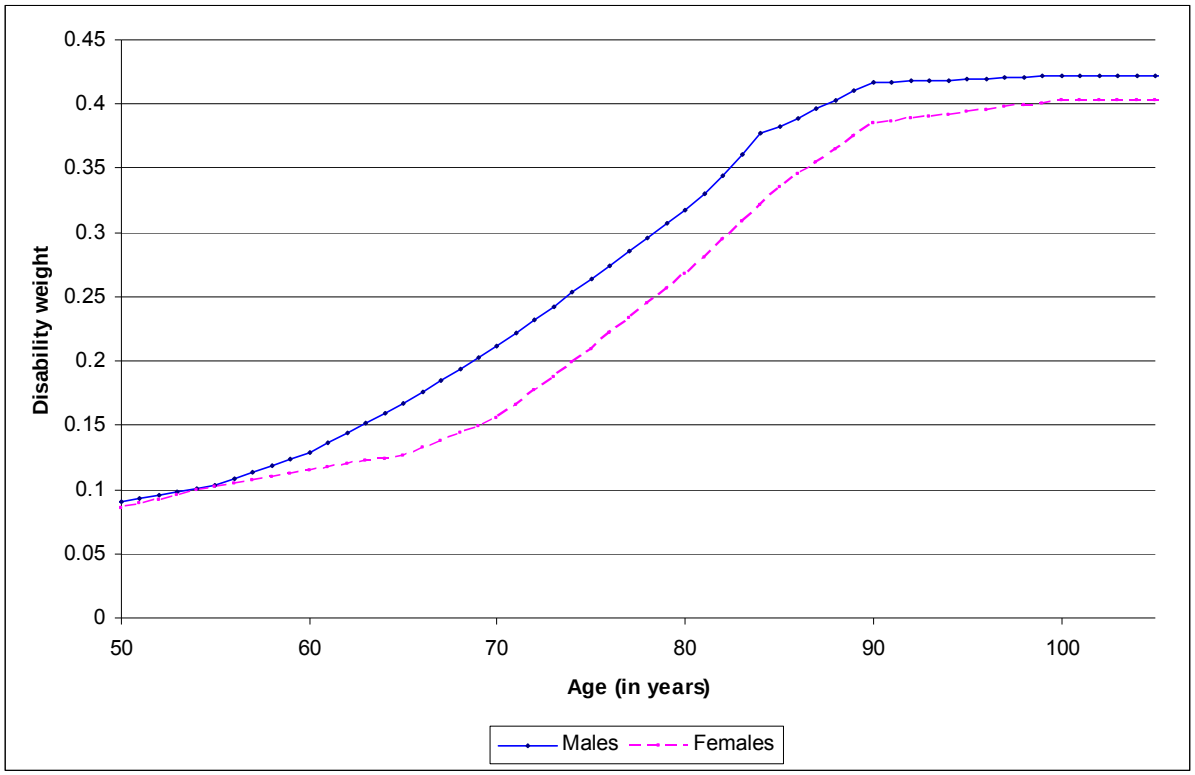
1.7 Key assumptions

The key assumptions that have been made in construction of the current analysis are as follows.

- If herpes zoster vaccine were to be included on the NIP, the target population would be Australians aged ≥ 50 years;
- The results from the SPS are directly applicable to the Australian population aged ≥ 50 years. Assumptions of effectiveness in persons aged 50-59 years of age are based on results of two studies demonstrating similar immunogenicity (not clinical equivalence) in this age group compared to those 60 years of age and older. Assumptions of equivalence between the refrigerator-stable formulation of ZOSTAVAX (as registered by the TGA) and the frozen formulation of ZOSTAVAX (used in the SPS) are based on results of a single, relatively small trial (N = 368) demonstrating similar immunogenicity (not clinical equivalence) across the formulations.
- Although trends favouring the vaccine were found in the proportion of patients with herpes zoster who developed post-herpetic neuralgia and in the rate of resolution of post-herpetic neuralgia beyond that afforded by the reduction in incidence of herpes zoster, the model assumes no difference in these parameters (i.e., it is assumed that that there is no reduction in PHN for vaccine recipients beyond that afforded by reducing the incidence of herpes zoster illness) because no statistically significant impact on these outcomes has been demonstrated in the Oxman et al (2005) report of the trial.
- The vaccine will be administered to 80% of the target population (which is equivalent to the proportion of the targeted population who have taken up influenza vaccine in Australia).
- The quality of life of a person aged ≥50 years who does not have herpes zoster is assumed to dependent on their age and sex. The distribution of disability weights applied by age and sex is shown in Figure 1. These disability weights are derived from the Australian Burden of Disease Study. Estimates of the total of Prevalent Years Lived with Disability (PYLD) from the burden of disease study for all conditions excluding herpes

zoster and post-herpetic neuralgia are divided by the population in each 5-year age and sex category. Disability weights for ages between each 5-year group were derived by linear interpolation.

Figure 1: Disability weights applied by age and sex for persons who do not have herpes zoster or post-herpetic neuralgia



- A health state where a person is aged ≥ 50 years and has either herpes zoster or post-herpetic neuralgia is assumed to be associated with an average disability weight of 0.15. These estimates are based on the results of a study that sought to elicit preference weights for herpes zoster related health states reported by Coplan et al (2004).
- Approximately 40% of patients developing herpes zoster will be prescribed a course of antiviral therapy (estimated using PBS utilisation statistics for antiviral therapies); approximately 3% of patients developing herpes zoster will be hospitalised for complications (Source: http://www.ncirs.usyd.edu.au/newsevents/r_macintyre_hz_aust.pdf [Accessed: 27 February 2008])
- The long term efficacy of the vaccine is unknown as the mean duration of surveillance for herpes zoster was only 3.13 years (median: 3.12 years; range: 1 day to 4.90 years). One analysis examining costs and benefits over 50 years presented below assumes that there is no decline in the efficacy of the vaccine for 50 years. In another analysis, it is assumed that the efficacy of the vaccine begins to decline (linearly) 5 years after administration and that the relative risk of herpes zoster in vaccine-treated persons versus placebo-treated persons reaches 1 (i.e., no incremental effectiveness) in Year 15.
- Costs and outcomes are discounted at 3% p.a.

Important uncertainties that are not addressed by the current analysis include:

- Subjects with a history of herpes zoster were excluded from recruitment to the key trial (SPS) and it is therefore not known whether results from this trial are generalisable to such individuals.
- Subjects with immunosuppression were excluded from recruitment to the key trial (SPS) and it is therefore not known whether results from this trial are generalisable to such individuals. This may be important as immunocompromised individuals are at especially high risk for the development of herpes zoster.
- Subjects who had previously received varicella vaccine were excluded from recruitment to the key trial and it is therefore not known whether results from this trial will be applicable to future Australian populations (that are more likely to include people who have been vaccinated against varicella due to the inclusion of varicella vaccine on the National Immunisation Program in 2005).
- The incidence of herpes zoster (and PHN) in the SPS may be higher than observed in Australian general practice due to the method of identification of cases in the trial. At enrolment, subjects were educated with regard to the signs and symptoms of herpes zoster and were urged to report new rashes or new unilateral pain. In addition, subjects were directed to contact an automated telephone-response system (ATRS) monthly for the administration of a questionnaire to detect signs and/or symptoms of herpes zoster.
- It is notable that, according to the protocol for the SPS, subjects clinically diagnosed with herpes zoster were offered, without cost, the antiviral drug famciclovir. Consequently, it is possible that the utilisation of antiviral medication in the SPS may be greater than would apply in Australian clinical practice. Patients with milder cases of herpes zoster may not present to a healthcare professional or may not present early enough to justify prescribing of antiviral medication. Greater use of antiviral medication in the SPS may mean that the incidence and severity of PHN observed in the trial will be less than would apply in Australian practice.
- In relation to an adverse events substudy of the SPS, it has been noted that, given the finding that more subjects in the vaccine group experienced serious adverse events than the placebo group (1.9% vs 1.3%, p=0.03), the expected number of additional adverse events that would have been expected in the vaccine arm of the trial would be 116 (0.6% × 19,254) whereas vaccination prevented only 53 cases of PHN. Therefore, the number and nature of serious adverse events is potentially clinically relevant. To date, no analysis or enumeration of the serious adverse events reports has been published.

1.8 Sensitivity Analysis

Sensitivity analysis around the results presented below have not been conducted to date. However, the sensitivity of the results of the analysis to the key assumptions will be examined and reported in due course. Sensitivity analysis will be conducted around assumptions in regard to:

- costs associated with administration of the vaccine;
- the age at which people will become eligible for herpes zoster vaccine;
- uptake rate for the vaccine;
- incidence of herpes zoster and post-herpetic neuralgia;

- the potential for variations in incidence of herpes zoster and post-herpetic neuralgia by age and sex;
- disutility associated with herpes zoster and post-herpetic neuralgia;
- costs associated with managing herpes zoster and post-herpetic neuralgia;
- vaccine efficacy;
- the potential for variations in vaccine efficacy by age and sex;
- durability of vaccine efficacy;
- costs and effects on quality of life associated with experiencing adverse events will be performed given that it has been noted that the expected number of additional adverse events is greater than the number cases of PHN avoided (see key assumptions section).

1.9 Results

The results of a trial-based analysis are presented in Table 1. Determination of the acceptability of the cost-effectiveness of the herpes zoster vaccine on the basis of this analysis is problematic due to difficulties in interpreting the metric used to report results.

Table 1: Results of a trial-based economic evaluation

	Vaccine arm	Placebo arm	Increment
Costs per person: o Vaccine costs	$150	$0	$150
Outcomes over 3.1 years: o Proportion of person with herpes zoster	315/19,270 (1.63%)	642/19,276 (3.33%)	-1.70%
o Proportion of persons with PHN lasting 90 days	27/19,254 (0.140%)	80/19,247 (0.415%)	-0.275%
Incremental cost per case of herpes zoster avoided over 3.1 years:			$8,824
Incremental cost per case of post-herpetic neuralgia avoided over 3.1 years:			$54,545

As discussed above, modelling has been used to: (i) apply the evidence from the SPS to the Australian context, (ii) extrapolate outcomes beyond the time horizon of the trial (from 3 years to 10 years and to 50 years); (iii) transform outcomes assessed in the trials (rates of patients with herpes zoster and post-herpetic neuralgia) to a metric that permits comparison of this preventive intervention with other interventions being examined in the ACE Prevention project (i.e., to disability-adjusted survival); and (iv) incorporate provision of resources that are used manage herpes zoster and post-herpetic neuralgia that was not assessed by the trial. Results of an analysis in the catch-up cohort, examining a 10-year time horizon and assuming no waning in the efficacy of the vaccine over time, are presented in Table 2. The results when the analysis is extrapolated to 50 years is summarised in Table 3. These results illustrate that the cost-effectiveness of the vaccine improves as a longer time horizon is considered. This is not unexpected given that costs occur all occur in the baseline year while health gains are accrued over time as cases of herpes zoster (and its complications) are avoided. Given that cost-effectiveness of the vaccine only begins to approach acceptable levels when long time horizons are considered, the long term efficacy of the vaccine becomes an important consideration. As discussed above, the mean duration of surveillance in the SPS was only 3.13 years thus assumptions that there is no waning of the efficacy of the vaccine may be optimistic. Results of a base case analysis assuming that

decline in the efficacy of the vaccine starts five years after vaccination and that the RR of herpes zoster reaches 1 by 15 years after vaccination are presented in Table 4.

Table 2: Results of a modelled economic evaluation with a time horizon of 10 years

	Vaccine arm	Placebo arm	Difference
Discounted costs per person over 10 years:			
o Vaccine costs	$120.00	$0	$120
o Costs of managing herpes zoster and PHN	$11.83	$20.07	-8.24
Total costs:	$131.83	$20.07	$111.76
Discounted outcomes over 10 years:			
o Life-years	7.8	7.8	0
o Quality-adjusted survival (in years)	6.367382	6.366629	0.000753
Incremental cost per quality-adjusted year of survival gained over 10 years:			$148,420

Table 3: Results of a modelled economic evaluation with a time horizon of 50 years

	Vaccine arm	Placebo arm	Difference
Discounted costs per person over 50 years:			
o Vaccine costs	$120.00	$0	$120
o Costs of managing herpes zoster and PHN	$21.80	$37.17	-$8.24
Total costs:	$141.80	$37.17	$104.63
Discounted outcomes over 50 years:			
o Life-years	14.6	14.6	0
o Quality-adjusted survival (in years)	11.345095	11.343698	0.001397
Incremental cost per quality-adjusted year of survival gained over 50 years:			$74,896

Table 4: Results of the base-case modelled economic evaluation, which assumes waning in the efficacy of the herpes zoster vaccine commencing 5 years after administration of the vaccine and continuing for 10 years until the relative risk of herpes zoster infection reaches 1 in Year 15

	Vaccine arm	Placebo arm	Difference
Discounted costs per person over 50 years:			
o Vaccine costs	$120.00	$0	$120
o Costs of managing herpes zoster and PHN	$29.26	$37.17	-$7.91
Total costs:	$149.26	$37.17	$112.09
Discounted outcomes over 50 years:			
o Life-years	14.6	14.60	0
o Quality-adjusted survival (in years)	11.344406	11.343698	0.000708
Incremental cost per quality-adjusted year of survival gained over 50 years:			$158,319

Results of two analysis equivalent to the analyses presented in Table 3 and Table 4 but conducted for a cohort of individuals aged 50 are presented in
Table 5 and Table 6, respectively. Comparing the two sets of analyses demonstrates that the results of the analysis are sensitive to the age profile of the cohort in whom the vaccine is assumed to be used.

Table 5: Results of the base-case modelled economic evaluation, which assumes no waning in the efficacy of the herpes zoster vaccine in a population of subjects aged 50

	Vaccine arm	Placebo arm	Difference
Discounted costs per person over 50 years:			

o Vaccine costs	$120.00	$0	$120
o Costs of managing herpes zoster and PHN	$31.66	$53.16	-$8.85
Total costs:	$151.66	$53.16	$111.15
Discounted outcomes over 50 years:			
o Quality-adjusted survival (in years)	17.015719	17.013725	0.001994
Incremental cost per quality-adjusted year of survival gained over 50 years:			$49,401

Table 6: Results of the base-case modelled economic evaluation, which assumes waning in the efficacy of the herpes zoster vaccine commencing 5 years after administration of the vaccine and continuing for 10 years until the relative risk of herpes zoster infection reaches 1 in Year 15 conducted in a population of subjects aged 50

	Vaccine arm	Placebo arm	Difference
Discounted costs per person over 50 years:			
o Vaccine costs	$120.00	$0	$120
o Costs of managing herpes zoster and PHN	$44.31	$53.16	-$8.85
Total costs:	$164.31	$53.16	$111.15
Discounted outcomes over 50 years:			
o Quality-adjusted survival (in years)	17.014523	17.013725	0.000799
Incremental cost per quality-adjusted year of survival gained over 50 years:			$139,203

1.10 Financial implications

In 2003, there were approximately 5,879,000 Australians aged 50 or more. Assuming an uptake rate of 80% for the herpes zoster vaccine in this target group and assuming a cost of $150 per person vaccinated, the total costs associated with vaccinating this group of individuals can be estimated to be approximately $705 million. Once the catch-up cohort is vaccinated, if 80% of people turning 50 are assumed to be vaccinated each year (i.e., approximately 214,000 people per year), annual costs are estimated to be approximately $32 million.

1.11 Discussion

According to the point estimates of the incremental cost effectiveness of the herpes vaccine (versus no vaccine) presented in Table 2, Table 3 and Table 4, herpes zoster vaccine does not appear to be acceptably cost-effective in a catch-up cohort if it is assumed that the threshold for acceptable cost-effectiveness is $50,000 per disability-adjusted year of survival gained. As can be seen if results presented in Table 3 are compared with results presented in Table 4, the incremental cost-effectiveness of the vaccine is extremely sensitive to assumptions of the long term efficacy of the vaccine. Analyses of uncertainty around the point estimates of the incremental cost-effectiveness ratios presented in the results section and analyses examining the sensitivity of results to changes in key assumptions will need to be conducted before any definitive conclusion with respect to the acceptability of the cost-effectiveness of herpes zoster vaccine can be reached.

1.12 References

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Attachment 1: Structure of the modelled economic evaluation