

PUBLIC SUMMARY DOCUMENT

Product: Temsirolimus, injection set containing 1 vial of powder for IV infusion 25 mg and 1 vial diluent, Torisel[®]

Sponsor: Wyeth Australia Pty Ltd

Date of PBAC Consideration: July 2008

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drugs Program) listing for the treatment of advanced renal cell carcinoma (RCC) in patients with a poor prognosis who meet certain criteria.

Highly Specialised Drugs are medications for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Temsirolimus was TGA registered on 4 June 2008 for the treatment of advanced renal cell carcinoma.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs Program) Private hospital authority required

Initial treatment (up to 3 months) as the sole PBS-subsidised therapy, except for the purposes of palliation, for adult patients with histologically or cytologically confirmed advanced renal cell carcinoma, who have at least three of the following six factors predictive of poor prognosis:

1. LDH more than 1.5 x upper limit of normal
2. Haemoglobin less than the lower limit of normal
3. Corrected calcium greater than 2.5 mmol/L
4. No more than 1 year since diagnosis until initiation of treatment
5. Karnofsky performance status (KPS) no greater than 70
6. At least 2 sites of metastatic disease

Continuing treatment beyond 3 months, as the sole PBS-subsidised therapy, except for the purposes of palliation, for patients who have received PBS-subsidised initial treatment with temsirolimus for advanced renal cell carcinoma and who have stable disease or responding disease as defined by RECIST criteria.

For PBAC's view of the requested listing, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Renal cell carcinoma is a form of kidney cancer that arises from the cells of the renal tubule. The management and prognosis of a patient with RCC is determined by the stage of the disease. Surgery is the only curative treatment option for localised RCC – radical nephrectomy is considered the gold-standard treatment for all patients with localised tumours. In patients with locally advanced or metastatic disease, nephrectomy may also be considered. As RCC progresses, the tumour grows and enlarges, and often spreads to adjacent organs.

However, most patients are diagnosed with advanced RCC, which is often refractory to treatment and associated with a poor prognosis.

Currently, three other agents including interferon alpha (IFN) are registered in Australia for the management of advanced RCC but none are PBS listed for this indication. Temsirolimus is an alternative treatment for patients with advanced RCC. Patients with advanced RCC receive best supportive care or are enrolled in special access programs or clinical trials.

6. Comparator

The submission nominated medroxyprogesterone (MPA) as proxy for placebo with best supportive care (BSC) as the main comparator, and provided an indirect analysis of temsirolimus versus BSC with IFN as the common comparator.

The PBAC considered that best supportive care was a valid comparator.

For PBAC's views, see Recommendation and Reasons.

7. Clinical Trials

The submission presented an indirect comparison of one randomised trial, Trial TEM 304, comparing temsirolimus 25 mg IV per week with IFN up to 18 mU three times per week subcutaneously in patients with advanced RCC and one randomised trial, Trial MRC RCC 2000, comparing IFN up to 10 mU three times per week subcutaneously with MPA 300 mg per day in advanced RCC. The submission presented a supplemental indirect comparison of Trial TEM 304 with a meta-analysis (Coppin 2006) of four IFN randomised trials.

The randomised trial and associated reports published at the time of submission, are as follows:

Trial ID	Protocol title/ Publication title	Publication citation
Randomised trials used in Section B		
Trial TEM 304 Hudes G et al.	Temsirolimus, interferon alpha, or both for advanced renal-cell carcinoma Clinical Study Report 3066K1-304-WW, 18 August 2006	N Engl J Med 2007;356:2271-2281
Trial MRC RCC	Interferon-alpha and survival in metastatic renal cell carcinoma: Early results of a randomized controlled trial	Medical Research Council Renal Cancer Collaborators Lancet 1999;353:14-17
Meta-analysis of trials		
Coppin 2006 (Cochrane) Coppin C, et al.	Immunotherapy for advanced renal cell cancer	Cochrane Database of Systematic Reviews 2004; Issue 3, updated 2006.

8. Results of Trials

The efficacy results from trial TEM 304 showed that there was a statistically significant difference in survival.

Efficacy results of Trial TEM 304 – temsirolimus and interferon arms only

Analysis	Result (95% CI)
Survival	

Comparison of time-to-first event curves	Median survival (months)	Temsirolimus = 10.9 (8.6, 12.7) Interferon = 7.3 (6.1, 8.8)
	CPH	HR = 0.73 (0.58, 0.92)
Progression-free survival by independent assessment		
Comparison of time-to-first event curves	Median PFS (months)	Temsirolimus = 5.5 (3.9, 7.0) Interferon = 3.1 (2.2, 3.8)
	CPH	HR = 0.73 (0.58, 0.92)

HR=hazard ratio, CPH=Cox proportional hazard model, PFS=Progression free survival

Efficacy results of Trial MRC RCC 2000: BSC with MPA versus interferon

Analysis		Result (95% CI)
Survival – 236 events: MPA-125 deaths, IFN-111 deaths		
Comparison of time-to-first event curves	Median survival (months)	IFN = 8.5 BSC = 6.0 Difference = 2.5 (0.5, 5.0)
	CPH	HR = 0.72 (0.55, 0.94)
Progression-free survival – 264 events		
Comparison of time-to-first event curves	Median PFS (months)	IFN = 4 BSC = 3 Difference = 1 (0.25, 2.5)
	CPH	HR = 0.72 (0.56, 0.92)

HR=hazard ratio, CPH=Cox proportional hazard model, PFS=Progression free survival

The results of the primary indirect comparison of Trial TEM 304 and Trial MRC RCC 2000, and the secondary indirect comparison of Trial TEM 304 and the Coppin (2006) meta-analysis are shown in the table below.

Summary of the results used in the indirect comparison

Trial	TEM vs IFN HR (95% CI)	TEM	IFN	BSC	BSC vs IFN HR (95% CI)	Indirect analysis (TEMvsBSC) HR (95%CI)
		Median survival (months)				
TEM 304	0.73 (0.58, 0.92)	10.9 (8.6, 12.7)	7.3 (6.1, 8.8)			0.53 (0.37,0.75) P=0.0004
MRC RCC 2000			8.5 (NR)	6.0 (NR)	1.39 (1.81,1.06)	
Coppin 2006			11.4	7.6	1.35 (1.59,1.14)	0.54 (0.41,0.72) P<0.0001

In light of the difference in median survival of the two interferon arms, 7.3 months in Trial TEM 304 and 8.5 months in Trial MRC RCC 2000, the submission “adjusted” for this difference by using the Trial TEM 304 figure of 7.3 months also for the Trial MRC RCC 2000 interferon arm and lowering the best supportive care arm figure for Trial MRC RCC 2000 by the same proportion. Thus, the value for Trial MRC RCC 2000 best supportive care arm is reduced from 6.0 months to 5.15 months [= 6*(7.3/8.5)]. The adjustment was made similarly for the supplemental indirect comparison with Coppin (2006). The adjusted median differences in overall survival were used in the trial-based economic evaluation. The results of these “adjusted” indirect comparisons are shown in the table below.

Results of the unadjusted and adjusted indirect comparisons of survival in Trial TEM 304 versus and Trial MRC RCC 2000 (primary) and in Trial TEM 304 and the Coppin meta-analysis (supplemental) using interferon as common comparator

Trial Analysis	TEM vs. IFN	TEM	IFN	BSC	BSC vs. IFN	Indirect estimate (TEM vs BSC)
	Median survival (months)					
TEM 304	3.6	10.9	7.3			
MRC RCC 2000 unadjusted			8.5	6.0	2.5	6.1
MRC RCC 2000 adjusted			7.3	5.15	2.15	5.75
Coppin 2006 unadjusted			11.4	7.6	3.8	7.4
Coppin 2006 adjusted			7.3	4.9	2.4	6.0

For trial TEM 304 the submission reported the Q-TWiST results . The Q-TWiST is a measure of quality of life over the time interval of the trial, similar to what is done over the time horizon of economic models. The Q-TWiST results demonstrated a quality adjusted life month gain of between 1 and 2 months, depending on the analysis used.

Quality of life (QoL) in Trial MRC RCC 2000 was captured with the Rotterdam Symptom checklist, a cancer quality-of-life instrument. Compliance was equal in both arms at approximately 50%. Statistically significant differences are reported at 4 weeks for 7 of 31 symptoms and at 12 weeks for 3 of 31 symptoms. At 6 months there was no statistically significant difference in any of the 31 symptoms assessed.

A benefit in survival for temsirolimus compared to BSC was likely although the magnitude of the benefit was difficult to determine. The quality of life comparison was made more difficult by the use of different assessment instruments in the two trials and inadequate data were presented to support the non-inferiority of temsirolimus compared with BSC in terms of quality of life.

Grade 3 or 4 adverse events occurred in 67% of patients in the temsirolimus group and 78% of patients in the IFN group. However, treatment emergent adverse events occurred in all patients in the trial. There was no formal comparison of safety between the Trial TEM 304 and Trial MRC RCC 2000.

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that temsirolimus is superior in effectiveness and superior in safety over interferon. The PBAC noted that superiority in survival had been shown in Trial TEM 304, but the data were insufficient to conclude superiority with respect to safety.

The submission also claimed that temsirolimus is superior in effectiveness to best supportive care and may be associated with more toxicity than best supportive care but not at the expense of quality of life.

For PBAC's views, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a stepped economic evaluation. The model estimated the cost-effectiveness of temsirolimus compared to best supportive care in advanced renal cell carcinoma patients with poor prognosis and also provided a comparison of temsirolimus and IFN in a stepped economic evaluation. The model employed a Markov-like structure with three primary health states – no progression, progression, and death. The model horizon was three years and used 36 one-month cycles. Patients received temsirolimus until progression. The model included only adverse events of grade 3 or 4 severity.

The submission estimated the base case incremental cost-effectiveness ratio to be >\$100,000 per quality of life year gained.

11. Estimated PBS Usage and Financial Implications

The financial cost/year to the PBS was estimated to be less than \$10M in Year 5.

12. Recommendation and Reasons

The PBAC agreed that BSC was a valid comparator despite the fact that the direct comparison of temsirolimus against IFN provides a higher standard of evidence than the indirect comparison with BSC using interferon as a common comparator. However, it was noted that IFN is not on the PBS as it was not considered effective or cost-effective for RCC.

The PBAC noted that temsirolimus was more effective when used as a single agent than when used in combination with IFN and that, in the event listing is recommended, the restriction should indicate that temsirolimus must be used as sole PBS-subsidised therapy.

The PBAC agreed that there was uncertainty about the magnitude of the treatment effect of temsirolimus compared with BSC because of the indirect comparison and the lack of exchangeability across the trials use to estimate the hazard ratios. The submission claims that temsirolimus is better than IFN which is, in turn better than BSC, but the indirect comparison which normalised IFN survival across the studies to estimate the magnitude of survival makes the analysis very uncertain. It was noted that in some studies survival in the IFN arm is 11.4 months, the current study 7.3 months, and in others 8.5 months. Therefore, the survival in the IFN arm depends on the inclusion criteria for the study. Even though, the sponsor acknowledged this in its pre sub-committee response by stating that the difference is due to the inclusion of different Memorial Sloan Kettering Cancer Centre (MSKCC) patient risk groups and also adjusted the survival data to allow for the indirect analysis, the PBAC considered that the residual uncertainty in the extent of clinical benefit was too large.

The PBAC noted that adverse events occurred at a statistically significant greater frequency in temsirolimus treated patients compared to IFN patients in Trial TEM 304 and concluded that the profile of side effects for temsirolimus was different to IFN, rather than that temsirolimus was better tolerated than IFN. However, the PBAC considered that the submission did not consider the relative harms in comparison with BSC, including their impact on incremental QALYs and cost-effectiveness. The PBAC also considered that there was uncertainty regarding the effect of temsirolimus on QoL, as the two trials in the submission used different QoL instruments.

It was also noted that the dose intensity of the drug is quickly lost if adverse events lead to delayed treatment which may impact on outcome and QoL.

The PBAC agreed, that the main areas of uncertainty in the economic analysis are the:

- Lack of exchangeability across trials in indirect comparison to estimate hazard ratios – particularly differences in IFN (common arm) dosing and extended period of time (10 years) between when trials were undertaken.
- Not reporting major sources of uncertainty within the trial period or their impact on cost effectiveness – e.g. not reporting a confidence interval for the temsirolimus-placebo treatment effect or absolute LY difference. The Pre-Sub-Committee Response states that it was not possible to determine confidence intervals for the temsirolimus-placebo effect in terms of overall survival as the confidence intervals associated with treatment effect of interferon over BSC were not reported.
- Challenges in estimating mean survival benefit.

The resulting base case incremental cost effectiveness ratio for temsirolimus over best supportive care > \$100,000 per QALY, was considered by the Committee to be both unacceptably high and unacceptably uncertain.

Therefore, the PBAC rejected the application on the basis of uncertain evidence of clinical effectiveness and an unacceptably high and uncertain incremental cost-effectiveness ratio.

Recommendation

Reject

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

The Sponsor will be considering the PBAC's advice.