

PUBLIC SUMMARY DOCUMENT

Product: Thalidomide, capsule, 50 mg Thalidomide Pharmion®

Sponsor: Celgene Pty Ltd

Date of PBAC Consideration: March 2009

1. Purpose of Application

The submission sought an extension to the current Section 100 Highly Specialised Drug listing to include treatment of patients newly diagnosed with multiple myeloma.

2. Background

At the March 2005 meeting, the PBAC recommended a Section 100 (Highly Specialised Drug) listing for thalidomide for the treatment of patients with relapsed/refractory multiple myeloma on the basis of a high, but acceptable cost-effectiveness ratio compared with a weighted average of a mixture of salvage treatments. Listing was effective from 1 February 2006.

3. Registration Status

Thalidomide was TGA registered on 13 March 2008 for:

Multiple Myeloma

- in combination with melphalan and prednisone for the treatment of patients with untreated multiple myeloma equal to or greater than 65 years or ineligible for high dose chemotherapy.
- in combination with dexamethasone for induction therapy prior to high dose chemotherapy with autologous stem cell rescue, for the treatment of patients with untreated myeloma.

Thalidomide is also TGA registered for the following indications:

- as monotherapy, for the treatment of multiple myeloma after failure of standard therapies;
- Erythema Nodosum Leprosum (ENL)
 - for the acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL).
 - not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis.
 - maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.

Thalidomide Pharmion is prescribed and dispensed through the Thalidomide Risk Management Program.

4. Listing Requested and PBAC's View

The sponsor proposed two (2) options for listing, with option 1 being the sponsors preferred listing.

Option 1

Private Hospital Authority Required

Treatment of a patient newly diagnosed with multiple myeloma.

Note: Patients receiving thalidomide under the PBS listing must be registered in the Thalidomide Risk Management Program.

Option 2

Private Hospital Authority Required

Treatment of a patient newly diagnosed with multiple myeloma who is ineligible for treatment with high dose chemotherapy or a stem cell transplant.

Note: Patients receiving thalidomide under the PBS listing must be registered in the Thalidomide Risk Management Program.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Multiple myeloma is a disorder in which malignant plasma cells accumulate in the bone marrow and produce immunoglobulin, usually monoclonal IgG or IgA (M-protein or paraprotein). It can be a rapidly progressing condition for which there is no cure. Current treatment for younger newly diagnosed patients includes high dose chemotherapy (HDC) followed by a stem cell transplantation (SCT).

Thalidomide would provide an alternative induction therapy regimen in patients undergoing HDC/SCT and would be an additional therapy in patients ineligible for HDC/SCT.

6. Comparator

For the patient population eligible for HDC/SCT, vincristine in combination with adriamycin was the nominated comparator. For the patient population ineligible to receive HDC/SCT, placebo was the nominated comparator. The PBAC considered the comparators were appropriate.

7. Clinical Trials

For the patient population ineligible for HDC/SCT, the submission presented five randomised trials comparing thalidomide (as part of a melphalan-prednisone-thalidomide (MPT) regimen, thalidomide dose range 100-400 mg/day) with placebo (as a melphalan and prednisone (MP) regimen) in patients with newly diagnosed multiple myeloma. For the patient population eligible for induction treatment prior to HDC/SCT, the submission presented four randomised trials comparing thalidomide (in different chemotherapy regimens, thalidomide dose range 200-400 mg/day) with various comparators in patients with newly diagnosed multiple myeloma.

All of the studies relating to patients ineligible for HDC/SCT had been published at the time of the submission, as follows:

Trial/First author	Protocol title	Publication Citation
Direct randomised trials		
Facon et al	Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial.	The Lancet, 370 (9594): 1209-1218, 2007.
	Author's Reply (The Lancet 2008).	The Lancet, 371: 984 – 985,

		2008.
Hulin et al	Melphalan-prednisone-thalidomide (MP-T) demonstrates a significant survival advantage in elderly patients ≥ 75 years with multiple myeloma compared with melphalan-prednisone (MP) in a randomized, double-blind, placebo-controlled trial, IFM 01/01. Comparison of melphalan-prednisone-thalidomide (MP-T) to melphalan-prednisone (MP) in patients 75 years of age or older with untreated multiple myeloma (MM). Preliminary results of the randomized, double-blind, placebo controlled IFM 01-01 trial.	ASH, Blood. 110: Abstract 75, 2007. Journal of Clinical Oncology ASCO Annual Meeting Proceedings, 25(18S): 8001, 2007.
Palumbo et al	Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial.	The Lancet, 367: 825-831, 2006.
Palumbo et al	Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized, controlled trial.	Blood Epublished Online: 1-25, 2008.
Rus and Palumbo et al	Thalidomide in front line treatment in multiple myeloma: serious risk of venous thromboembolism and evidence for thromboprophylaxis.	Journal of Thrombosis and Haemostasis, 2:2063-5, 2004.
Wijermans et al	Melphalan prednisone versus melphalan prednisone thalidomide in induction therapy for multiple myeloma in elderly patients: first interim results of the Dutch Cooperative Group HOVON.	European Hematology Association (EHA) 13th Congress, Copenhagen, 2008.
Waage et al	Melphalan-prednisone-thalidomide to newly diagnosed patients with multiple myeloma: a placebo controlled randomised phase 3 trial.	Blood 110(Abstract 78), 2007.
Gulbrandsen et al	A randomised placebo controlled study with melphalan prednisone versus melphalan prednisone thalidomide: quality of life and toxicity.	European Hematology Association (EHA), Copenhagen, Denmark, 2008.
Meta-analyses of direct randomised trials		
Hicks et al	A meta-analysis and systematic review of thalidomide for patients with previously untreated multiple myeloma.	Cancer Treatment Reviews, 34 (5): 442-452, 20, 2008.

All of the studies relating to patients eligible for HDC/SCT had been published at the time of the submission, as follows:

Trial/First author	Protocol title	Publication Citation
Direct randomised trial(s)		
Rajkumar et al	Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: A clinical trial coordinated by	Journal of Clinical Oncology, 24(3): 431-436, 2006.

al (2008) (HOVON-50/ GMMG-HD3)	the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma.	
Lokhorst, H	Phase III Randomized Study of Doxorubicin, Dexamethasone, and High-Dose Melphalan With or Without Thalidomide in Patients With Multiple Myeloma.	National Institutes of Health, Clinical Trials Gov (http://www.clinicaltrials.gov), 2003.
Breitkreutz, et al	Thalidomide in newly diagnosed multiple myeloma: Influence of thalidomide treatment on peripheral blood stem cell collection yield.	Leukemia, 21(6): 1294-1299, 2007.
Goldschmidt et al	Joint HOVON-50/GMMG-HD3 randomized trial on the effect of thalidomide as part of a high-dose therapy regimen and as maintenance treatment for newly diagnosed myeloma patients.	Annals of Hematology, 82(10): 654-659, 2003.
Meta-analyses of direct randomised trials		
Hicks et al	A meta-analysis and systematic review of thalidomide for patients with previously untreated multiple myeloma.	Cancer Treatment Reviews, 34(5): 442-452, 2008.

8. Results of Trials

The results of the trials for the ineligible HDC/SCT patient population are presented below:

	Facon 2007		Hulin 2007		Palumbo 06/08		Wijermans 2008		Waage 2007	
	MPT n=125	MP n=196	MPT n=113	MP n=116	MPT n=167	MP n=164	MPT n=152	MP N=149	MPT n=182	MP n=175
Overall survival										
Median months (s.e.)	51.6 (4.5)	33.2 (3.2)	45.3 (1.6)	27.7 (2.1)	45.0	47.6	NR	NR	29	33
HR (95%CI)	0.59 (0.46, 0.81)		0.66 (0.44, 1.00)		1.04 (0.76, 1.44)		NR		NR	
p-value	0.0006		0.03		0.79		0.28		NS	
PFS										
Median months (s.e.)	27.5 (2.1)	17.8 (1.4)	24.1 (2.0)	19.0 (1.4)	21.8	14.5	NR	NR	16	14
HR (95%CI)	0.51 (0.39, 0.66)		NR		0.63 (0.48, 0.81)		NR		NR	
p-value	<0.0001		0.001		<0.001		0.08		NS	
Response rate (CR+VGPR+PR)										
n (%)	91 (85)	78 (51)	103 (91)	45 (39)	115 (68.9)	78 (47.6)	96 (63)	70 (47)	76 (42)	49 (28)
p-value	<0.001		<0.001		<0.001		<0.001		0.006	
RR (95%CI)	1.67 (1.40, 1.99)		2.35 (1.86, 2.97)		1.45 (1.20, 1.75)		1.34 (1.09, 1.66)		1.49 (1.11, 1.99)	
RD (95%CI)	0.34 (0.24, 0.45)		0.52 (0.42, 0.63)		0.21 (0.11, 0.32)		0.16 (0.05, 0.27)		0.14 (0.04, 0.24)	
NNT (95% CI)	3 (2, 4)		2 (2, 2)		5 (3, 9)		6 (4, 20)		7 (4, 25)	

Abbreviations: s.e.: standard error, PFS: progression-free survival, RR: relative risk, RD: risk difference, NNT: number needed to treat, NS: not significant, NR: not reported, CR: complete response, VGPR: very good partial response, PR: partial response, HR: hazard ratio.
 Bolded typography indicates statistically significant differences

The addition of thalidomide to the MP regimen resulted in increased overall survival in two (Facon (2007), Hulin (2007)) of the three trials in which this was the primary outcome (Facon (2007), Hulin (2007) and Waage (2007)). Information regarding the Waage (2007) trial was lacking, although the authors suggested that the lack of efficacy might be due to a number of early deaths among elderly patients with Stage I disease treated in the MPT arm.

The addition of thalidomide to the MP regimen resulted in statistically significant progression-free survival differences between treatment groups in favour of thalidomide for Facon (2007), Hulin (2007) and Palumbo (06/08) at the 1% level of significance and at the 10% level of significance for Wijermans (2008). A non-statistically significant difference was observed for progression-free survival in Waage (2007). The PBAC noted as progression free survival (PFS) was a secondary outcome of the Waage (2007) trial, the trial might not have been powered to detect a difference in this outcome.

Response rates were statistically significantly greater for patients in whom thalidomide was added to the MP regimen compared with those who received MP alone in all trials.

The results of the trials for the eligible HDC/SCT patient population are presented below:

	Rajkumar 2006		Lokhorst 2008		Barlogie 2006		Macro 2006	
	TD n=99	D n=100	TAD n=201	VAD n=201	TD comb. n=314	D comb. n=337	TD n=100	VAD n=104
≥PR, n (%)	62 (62.6)	41 (41)	145 (72)	109 (54)	187 (60)	136 (40)	NR	NR
RD % (95% CI)	22 (8, 35)		18 (9, 27)		19 (12, 27)		-	
p-value	0.0017		<0.001		<0.001		-	
≥VGPR, n (%)	NR	NR	66 (33)	30 (15)	NR	NR	35 ^b (34.7)	13 ^b (12.6)
RD % (95% CI)	-		18 (10, 26)		-		23 (11, 34)	
p-value	-		<0.001		-		0.002	
CR + VGPR + PR, n (%)	62 (62.6)	41 (41)	145 (72.0)	109 (54.0)	187 (60.0)	136 (40.0)	NR	NR
p-value	0.0017		<0.001		<0.001		NA	
RR (95%CI)	1.53 (1.15,2.02)		1.33 (1.14, 1.55)		1.48 (1.26, 1.73)		NA	
RD (95%CI)	0.22 (0.08, 0.35)		0.18 (0.09, 0.27)		0.19 (0.12, 0.27)		NA	
NNT (95% CI)	5 (3, 13)		6 (4, 11)		5 (4, 8)		NA	

Abbreviations: TD: thalidomide and dexamethasone, D: dexamethasone, VAD: vincristine, Adriamycin and dexamethasone, PR: partial response, CR: complete response, VGPR: very good partial response, RR: relative risk, RD: risk difference, NNT: number needed to treat, CI: confidence interval, NR: not reported, NA: not applicable.

The primary outcome for the induction setting presented by the submission was limited to response rates prior to HDC/SCT. Best response to treatment was the primary outcome in Rajkumar (2006), with Lokhorst (2008) and Macro (2006) also having primary outcomes

based on response rates. Statistically significant differences between treatment groups in favour of thalidomide were observed in all four trials for patients achieving at least a partial response (PR). Additionally, Rajkumar (2006) and Barlogie (2006) showed a statistically significantly higher rate of CR following thalidomide treatment.

Overall response rate was the primary outcome in Lokhorst (2008), with Rajkumar (2006) and Macro (2006) also having response rate primary outcomes. Statistically significant differences between treatment groups in favour of thalidomide were observed in the three trials. Additionally, Rajkumar (2006) and Barlogie (2006) showed a statistically significantly higher rate of complete response (CR) following thalidomide treatment.

Five-year event-free survival (defined as time to disease progression, relapse or death from any cause from enrolment) was the primary outcome measure for the Barlogie (2006) trial. The thalidomide group had higher five year event free survival compared with the control group (56% versus 44%, respectively; $p < 0.01$).

Overall survival was reported for both Barlogie (2006) and Rajkumar (2006). Mean survival was 70.1 weeks (standard error=27.7) for the thalidomide and dexamethasone (TD) group and 68.1 weeks (standard error = 28.7) for the dexamethasone (D) group in the Rajkumar (2006) trial. This was not statistically significant different.

A post-hoc analysis of eight year survival data was conducted as part of the Barlogie trial (Barlogie et al (2008)). The overall eight year survival estimates were 56% for the thalidomide group compared with 45% in the control group ($p=0.09$). It was reported that the lack of difference in overall survival may be due in part to significantly shorter survival after relapse in the thalidomide group than in the control group (median 1.1 years versus 2.7 years; $p = 0.001$).

For patients ineligible for HDC/SCT, adverse events were reported more frequently in patients treated with MPT compared with those receiving MP. Adverse Events (AEs) of note were those which have been previously associated with the use of thalidomide – notably peripheral neuropathy, neutropenia, rash, somnolence, deep vein thrombosis (DVT) and constipation. This increased occurrence of AEs was generally associated with a higher rate of treatment discontinuation among MPT treated patients compared with MP. Despite this, there was no difference in AE related deaths among the thalidomide treated patients, compared with those who received MP alone.

For patients eligible for HDC/SCT, AEs were reported more frequently in patients treated with TD, compared with those receiving dexamethasone alone or in combination. As expected, skin, neurological, cardiac and thromboembolic events have been identified previously as potential adverse reactions to thalidomide and events of this type were generally more frequently experienced in the thalidomide groups. This increased toxicity did not lead to more deaths in thalidomide-treated patients.

9. Clinical Claim

The submission claimed that for patients ineligible for HDC/SCT, thalidomide in combination with melphalan and prednisone was superior in terms of comparative effectiveness and inferior in terms of comparative safety over melphalan and prednisone alone.

The PBAC considered that this was reasonable but considered that there is some uncertainty about the size of the survival benefit.

For patients eligible for induction treatment prior to HDC/SCT, the submission claimed that thalidomide in combination with dexamethasone was superior in terms of comparative effectiveness and inferior in terms of comparative safety over the group of therapies currently used in the induction setting.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

A three-step economic evaluation was presented for the ineligible HDC/SCT patient population (referred to as the MPT model) and a cost-per-responder model was presented for the HDC/SCT eligible patient population.

The MPT stepped model was a decision analytic model and involved the within trial truncated overall survival from the Facon (2007) trial presented as cost per life year gained. Step two extrapolated the survival based on a Weibull function to a lifetime horizon of fifteen years.

Step three incorporated quality of life using published utility values obtained from van Agthoven (2006)¹. The key driver of the MPT model was the cost of thalidomide and the extrapolated survival estimate using the Weibull method. Sensitivity analyses using the straight line extrapolation method returned a cost per QALY in the range of \$15,000 – \$45,000 compared with a lower estimate for the Weibull extrapolation (which was in the same range of \$15,000 - \$45,000).

In patients eligible for transplant, for the cost per responder analysis, the submission used direct trial-based data from Macro (2006) as the input to the evaluation. The outcome was the proportion of patients achieving at least a very good partial response (VGPR) to induction treatment therapy over 3 cycles (3 months' treatment duration). The difference in treatment response across the two treatment groups (TD versus VAD) was used as the incremental response. No discounting was applied as the duration of the model is less than one year. Utilising corrected values for the refill cost of drug delivery into a venous catheter port, the estimated incremental cost per responder was in the range of \$15,000 – \$45,000.

11. Estimated PBS Usage and Financial Implications

The submission estimated in Year 5 the financial cost/year to the PBS to be between \$10 – \$20 million in Year 5.

12. Recommendation and Reasons

¹ van Agthoven et al (2004), A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma: a prospective randomised phase III study, *European Journal of Cancer* 40: 1159-1169, 2004.

The PBAC recommended an extension to the Section 100 listing for thalidomide to include the treatment of a patient newly diagnosed with multiple myeloma (first-line setting) on the basis of acceptable cost-effectiveness at the current rather than the requested price.

Of the two options nominated by the sponsor for PBAC consideration, the PBAC considered that Option 1 (which includes patients eligible and ineligible for high dose chemotherapy followed by stem cell transplantation (HDC/SCT)) to be the most clinically appropriate. The PBAC considered that it is not possible to accurately forecast for all patients at diagnosis whether a SCT will be performed. Given this, it is not appropriate or equitable to categorise patients as eligible or ineligible for SCT at diagnosis for the purpose of a PBS indication.

Based on the clinical trial data from patients nominated as ineligible for HDC/SCT, the PBAC considered that the submission's therapeutic claims were reasonable, i.e., that compared with melphalan and prednisone alone (MP), thalidomide in combination with melphalan and prednisone (MPT) is superior in terms of comparative effectiveness and inferior in terms of comparative safety. However, the PBAC also considered that there is some uncertainty about the size of the survival benefit.

The PBAC noted that a three-step economic evaluation (referred to as the MPT model) was presented for the ineligible HDC/SCT patient population in terms of incremental cost per extra life-year gained. The PBAC further noted that the trial data upon which this economic evaluation is based are from the most favourable of the five randomised trials, the Facon (2007) trial and hence may overestimate the true survival benefit. The key drivers of the MPT model are the cost of thalidomide and the extrapolated survival using the Weibull method, and that the latter may also have overestimated the overall survival of patients. Sensitivity analyses undertaken using a more conservative straight line extrapolation method returned an incremental cost effectiveness ratio (ICER) per QALY in the \$15,000 – \$45,000 range compared with a lower estimate for the Weibull extrapolation (which was also in the \$15,000 - \$45,000 range). The PBAC considered that the true estimate of the ICER in terms of incremental life-years gained was probably between the two point estimates and towards the higher estimate if the Facon-based trial results were also an overestimate of survival.

The PBAC noted that only the disutility of peripheral neuropathy as an adverse effect of thalidomide treatment is included in the model. Disutilities associated with other adverse events such as constipation and somnolence were not considered. The pre-sub-Committee response argued that the study from which the utilities are derived (van Agthoven et al. 2004) permitted treatment with vincristine, adriamycin and dexamethasone (VAD), cyclophosphamide and melphalan, and as such, the utility values reflect the disutility of adverse events associated with the treatment of multiple myeloma. The PBAC considered that the disutilities due to thalidomide toxicity had not been fully considered in the model, requiring adjustment in sensitivity analyses.

The PBAC noted that the costs of concomitant bisphosphonate therapy were excluded in both arms of the model. The Pre-Sub-Committee Response assumed that there is no long-term difference in bisphosphonate use between the two groups because the average survival for the MPT (54.5 months) and MP (36.7 months) are well beyond two years. The PBAC considered that this statement is incorrect and that failure to include true bisphosphonate costs underestimates the ICER.

The PBAC agreed that each of these concerns increased the uncertainty of the ICER, and suggested that the base case presented was more favourable than the true estimate. Although the sponsor's Pre-PBAC Response argues that the sensitivity analyses indicate that even allowing for some of this uncertainty, the ICER per QALY is no more than \$45,000, the PBAC noted that these were not comprehensive because not all relevant disutilities and costs were considered in economic model, and the most favourable base-case trial data were used.

Regarding trial-based data from patients receiving induction treatment prior to a planned HDC/SCT, the PBAC noted that no statistically significant differences in overall survival were reported. The PBAC accepted that any benefit of thalidomide over its comparators for the most relevant outcome (survival) in patients who had HDC/SCT is uncertain. For the most mature study (Barlogie et al (2008)), a published post-hoc analysis of the survival data was included, but these results could have been confounded. Nevertheless, the PBAC noted that the post-hoc analysis of eight-year survival data conducted as part of the Barlogie trial reported that the lack of difference in overall survival (56% thalidomide group compared with 45% control group) may be due in part to significantly shorter survival after relapse in the thalidomide group than in the control group (median 1.1 years versus 2.7 years; $p=0.001$). However, the PBAC did also note that the design of the available studies mitigated against drawing conclusions concerning overall survival benefits.

Thus, despite a significant advantage for thalidomide and dexamethasone over dexamethasone alone in terms of response rates, the PBAC did not accept that this had convincingly been shown to predict an overall survival benefit. The PBAC did note that thalidomide does improve response rates in SCT-eligible trial participants to as great a degree or extent as observed for SCT-ineligible patients where a survival advantage was demonstrated.

The PBAC noted that an analysis reporting incremental cost per extra responder was presented for the HDC/SCT eligible patient population. For this analysis, the submission used direct trial-based data from Macro (2006) as the input to the economic evaluation. The PBAC considered that this economic evaluation did not form an adequate basis to assess overall cost-effectiveness in terms of the key patient relevant outcome (improved survival). The PBAC noted that the cost per responder was highly sensitive to the type of comparator and number of cycles of thalidomide and also very likely sensitive to the time-point chosen to measure response. Therefore, this did not allow a fair comparison between different therapies.

Overall, across both subgroups in the first-line setting for multiple myeloma, the PBAC considered that there was an acceptable clinical basis to recommend the listing of thalidomide, but the Committee did not accept that acceptable cost-effectiveness had been demonstrated at the price requested. The PBAC therefore recommended approval at the current price of thalidomide.

The PBAC acknowledged that thalidomide was effective in all stages of multiple myeloma and that its use is limited by cumulative toxicity. The PBAC noted that if thalidomide is PBS-subsidised in first-line therapy, then there will be less use of thalidomide in second and subsequent lines, as each patient will have a ceiling with respect to total lifetime exposure due to cumulative toxicity or to the expiry of clinical benefit.

Recommendation

THALIDOMIDE, capsule, 50 mg.

Replace the current restriction with the following:

Restriction: Caution: Thalidomide is a category X drug and must not be given to pregnant women. Pregnancy in female patients or in the partners of male patients must be avoided during treatment and for 1 month after cessation of treatment.

Section 100 (Highly Specialised Drug)
Private Hospital Authority Required
Multiple myeloma.

Note: Patients receiving thalidomide under the PBS listing must be registered in the Thalidomide Risk Management Program.

Pack size: 28

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

Celgene accepts the recommendation made by the PBAC and welcomes this expanded access to thalidomide for all patients with multiple myeloma.