PUBLIC SUMMARY DOCUMENT
Product: Lenalidomide, capsules, 5 mg, 10 mg, 15 mg and 25 mg, Revlimid®
Sponsor: Celgene Pty Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application

To seek a Section 100 (Highly Specialised Drug) listing for the treatment of patients with relapsed/refractory multiple myeloma.

Highly specialised drugs are medicines 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 was the first time lenalidomide had been considered by the PBAC.

3. Registration Status

Lenalidomide was registered by the TGA on 20 December 2007 and is indicated for use in combination with dexamethasone in patients with multiple myeloma whose disease has progressed after one therapy.

4. Listing Requested and PBAC's View

Section 100 Private Hospital Authority Required

Relapsed/refractory multiple myeloma in combination with dexamethasone in a patient who has undergone at least one other therapy.

A patient is considered to be refractory to treatment who:

- is unable to achieve a reduction (< 25% decrease in M-paraprotein levels), or at least control (no increase) in initial multiple myeloma activity despite receipt of at least two cycles of a treatment for multiple myeloma at therapeutic levels ; or
- is unable to receive therapeutic levels of a treatment for multiple myeloma due to reasons of treatment intolerance or contraindication.

A patient is considered to have relapsed multiple myeloma who has progressive disease (> 25% increase in M-paraprotein levels, development of new lytic lesions, or progressive of existing lesions) after having achieved a response to their prior therapy.

No repeats will be authorised for females of childbearing potential. Up to two repeats will be authorised for all other patients.

Caution

Lenalidomide 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 one month after cessation of treatment with lenalidomide.

The PBAC noted that, if listed as requested, a restriction similar to that for thalidomide would be appropriate.

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. It is a chronic and disabling condition with no cure. Lenalidomide would provide an alternative treatment option for patients with relapsed/refractory multiple myeloma.

6. Comparator

The submission nominated thalidomide as the main comparator and bortezomib as the secondary comparator. The PBAC accepted that when used in place of thalidomide, thalidomide is the appropriate comparator. However, lenalidomide may be used in patients who have previously failed thalidomide. In this patient population bortezomib is the appropriate comparator.

7. Clinical Trials

The basis of the submission for the comparison of lenalidomide versus thalidomide were single arms of two direct randomised comparative trials with lenalidomide plus dexamethasone vs. placebo plus dexamethasone and two cohort studies with thalidomide plus dexamethasone. There was no common comparator for the lenalidomide and the thalidomide trials.

The thalidomide trials were controlled cohort analyses and therefore were neither randomised nor blinded. The PBAC was advised that the scientific basis of the comparison is of a much lower quality than is usually required to sustain a case for superiority.

The basis of the comparison with bortezomib was an indirect comparison of two lenalidomide plus dexamethasone vs. placebo plus dexamethasone trials (the same arms as in the comparison with thalidomide) compared with one bortezomib and dexamethasone trial, which had a randomised unblinded design, comparing bortezomib with high dose dexamethasone.

A list of the published trials and studies provided in the submission is presented in table below.

Trial/First author	Protocol title/Publication title	Publication citation
Lenalidomide		
Weber DM, et al (Study 009)	Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America.	N Engl J Med 357 2133-2142, 2007
Dimopoulos M, et al (Study 010)	Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma.	N Engl J Med 357 2123-2132, 2007
Thalidomide		
Palumbo A et al	Efficacy of low-dose thalidomide and dexamethasone as first salvage regimen in multiple myeloma.	The Hematology Journal 2004; 5:318-324.
Offidani M et al	Thalidomide-dexamethasone plus pegylated liposomal doxorubicin vs. thalidomide-dexamethasone: A case-matched study in advanced multiple myeloma.	European Journal of Haematology 2007; 78(4):297-302

Bortezomib		
Richardson PG et al	Bortezomib or high dose dexamethasone for relapsed multiple myeloma.	N Engl J Med 352(24): 2487-2498, 2005

8. Results of Trials

The primary outcome for the lenalidomide trials was time to progression. In both trials, the median time to progression was significantly longer in the lenalidomide plus dexamethasone arm compared with the dexamethasone only arm. The size of the difference was about 20 – 25 weeks.

The primary outcome for the APEX trial was time to progression, similar to the primary outcome of the lenalidomide trials. The results of lenalidomide and bortezomib on time to progression across the direct randomised trials are shown in the table below.

	Study 009		Study 010		APEX	
	LEN + DEX	**DEX**	**LEN + DEX**	**DEX**	**BORT**	**DEX**
N	170	171	176	175	315	312
Progressed n (%) **Censored** n (%)	44 (25.9) 126 (74.1)	98 (57.3) 73 (42.7)	39 (22.2) 137 (77.8)	99 (56.6) 76 (43.4)	n.r.	n.r.
TTP (weeks)[a] Median (95% CI) Median (published)[b] Min, Max	 48.1 0.0, 60.1	 20.4 0.0, 57.0	 49.0 0.0, 44.7	 20.4 0.3, 48.1	 26.8 (21.2, 29.9)	 15.2 (12.1, 18.2)
Hazard rate ratio[a] As published *Hazard ratio*	 2.86 (2.13 to 3.70) ***0.35* *(0.27 to 0.47)*		 2.85 (2.16 to 3.76) ***0.35* *(0.27 to 0.46)*		 0.55 (0.44, 0.69)	
Log-rank test p-value	<0.001		<0.001		<0.001	

Notes: n.e., not estimable; CI, confidence interval; HR, hazard ratio.

[a]results for the APEX study were reported as months, converted to weeks by multiplying by 4.33. HR is for risk of progression with bortezomib over that for dexamethasone alone, and is the reverse for lenalidomide.

[b]The time of analysis was when the study was unblended. This was after a median treatment period of 17 months in both studies.

**the trial abstracts and published reports used the alpha for the placebo arm in the numerator of the calculation of HR, which is the inverse to the standard reporting of HR. The usual method applied to the published results is shown in italics.

The pooled median time to progression was 41 weeks for lenalidomide plus DEX compared with 20 weeks for DEX treatment only.

The PBAC noted time to progression was not available for the thalidomide studies, neither of which included a DEX alone arm to serve as a common reference. The Offidani study was not informative for assessing the effect of thalidomide, since both arms of the study included thalidomide and the difference between them was the addition of conventional chemotherapy in one arm.

In the APEX trial the time to progression was 26 weeks for bortezomib and 15 weeks for DEX.

The PBAC noted that progression-free survival was similar between lenalidomide and thalidomide.

The secondary outcome in the lenalidomide studies, which was used in the economic evaluation, was overall survival. The submission presented updated results from the most recent analysis for Study 009 and Study 010.
The submission stated that the data suggest that the median survival for lenalidomide treated patients is above that of thalidomide: based on differences with the Palumbo study and the Offidani study.

The PBAC had concerns with this extrapolation for several reasons:

- direct comparison of survival times cannot be made reliably across studies without a common reference;
- the difference in median survival with thalidomide plus DEX compared with conventional chemotherapy (i.e. possibly attributable to thalidomide) is about 6 months (Palumbo); and
- the Offidani did not compare a thalidomide-treated group with a non-thalidomide-treated group, and therefore the survival advantage in this study should be attributed to the addition of conventional chemotherapy, not to thalidomide itself.

The overall survival for bortezomib was shorter compared with lenalidomide plus DEX. The hazard ratios for overall survival relative to DEX do not differ between the lenalidomide plus DEX and bortezomib trials, and are 0.77 vs. dexamethasone.

With regard to comparative toxicity, an indirect comparison between lenalidomide and thalidomide with a common comparator could not be made. The table below presents the grade 3 and 4 adverse effects observed in the lenalidomide trials, which were notably different between the two treatment arms.

Grade 3/ 4 adverse events in Studies 009 and 010*

	Study 009				**Study 010**			
Event	**Len+Dex (N = 177)**		**Dex (N = 175)**		**Len + Dex (N=176)**		**Dex (N=175)**	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
	number (percent)							
Hematologic disorder								
Neutropenia	62 (35)	11 (6.2)	6 (3.4)	2 (1.1)	44 (25)	8 (4.5)	4 (2.3)	0
Anaemia	19 (10.7)	4 (2.3)	6 (3.4)	3 (1.7)	14 (8.0)	1 (0.6)	12 (6.9)	0
Thrombocytopenia	24 (13.6)	2 (1.1)	12 (6.9)	0	17 (9.7)	3 (1.7)	7 (4.0)	3 (1.7)
Febrile neutropenia	5 (2.8)	1 (0.6)	0	0	5 (2.8)	1 (0.6)	0	0
Infection								
Pneumonia	19 (10.7)	3 (1.7)	10 (5.7)	5 (2.9)				
All other infection†	33 (18.6)	5 (2.8)	16 (9.1)	5 (2.9)	15 (8.5)	2 (1.1)	9 (5.1)	0
Vascular disorder								

	Study 009				Study 010			
Event	**Len+Dex (N = 177)**		**Dex (N = 175)**		**Len + Dex (N=176)**		**Dex (N=175)**	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
	number (percent)							
Deep-vein thrombosis	21 (11.9)	0	6 (3.4)	0	6 (3.4)	1 (0.6)	5 (2.9)	1 (0.6)
Pulmonary embolism	1 (0.6)	5 (2.8)	0	1 (0.6)	2 (1.1)	6 (3.4)	1 (0.6)	1 (0.6)
Venous thromboembolism‡	21 (11.9)	5 (2.8)	5 (2.9)	1 (0.6)	13 (7.4)	7 (4.0)	6 (3.5)	2 (1.1)

Notes: * Listed are data that were available on December 31, 2005. Percentages may not total 100 because of rounding.
† This condition was also described in the following terms: infections not otherwise specified, pneumonia, upper respiratory tract infection, upper respiratory viral infection, sepsis, bacterial infection, urinary tract infection, pharyngitis, nasopharyngitis, febrile neutropenia, oral candidiasis, oral fungal infection, primary atypical pneumonia, fungal sinusitis, herpes simplex, herpes zoster, herpes encephalitis, herpes viral infection, cytomegalovirus pneumonia, and viral infection.
‡ This condition was also described in the following terms: deep-vein thrombosis, pulmonary embolism, pulmonary infarction, thrombosis, phlebothrombosis, thrombophlebitis, superficial thrombophlebitis, venous thrombosis, thromboembolism, splenic-vein thrombosis, phlebitis, and superficial phlebitis.

The submission stated that based on trial data, the incidence of neuropathy appears lower with lenalidomide than thalidomide.

The comparison of the lenalidomide and bortezomib treatments indicates that the overall incidence of adverse events did not differ between them. However, the pattern of those events is different: lenalidomide treatment appears to be associated with significantly more neutropenia, insomnia and muscle cramps; bortezomib treatment appears to be associated with significantly more diarrhoea, nausea, peripheral neuropathy, vomiting, pyrexia, thrombocytopenia, cough, paraesthesia and bone pain.

9. Clinical Claim

The submission described lenalidomide as superior to thalidomide in terms of comparative effectiveness with a different safety profile.

The submission described lenalidomide as a more effective and well tolerated treatment than bortezomib.

Overall, the PBAC concluded there is great uncertainty about the relative clinical benefits of lenalidomide in comparison with either thalidomide or bortezomib, and that the three drugs have different toxicities.

With respect to the comparison between lenalidomide and thalidomide, the lack of a common reference precluded direct comparison of time to progression or overall survival, and this, together with the poor quality of the thalidomide studies makes any conclusions of superiority of one treatment over the other extremely unreliable.

With respect to the comparison between lenalidomide and bortezomib, while no differences were observed in the hazard rates for overall survival, a formal comparison had not been carried out.

10. Economic Analysis

A modelled economic evaluation was presented. The model calculated years of life lived and progression-free years of life lived for lenalidomide and thalidomide, using the survival data from the trials (three years), extrapolated for another three years for a total time horizon of six years. Most of the difference in years of life lived was from the within-trial data. Health benefits were based on the years of life lived, while the treatment costs are driven by the progression free years of life lived. The model structure was considered appropriate.

The incremental cost per life year gained (as calculated in the submission) for lenalidomide in place of thalidomide for the treatment of patients with relapsed/refractory multiple myeloma was between $45,000 and $75,000 (discounted). This increased using the updated base case but remained within the same range.

The submission calculated an incremental cost per Quality-Adjusted Life-Year (QALY) gained of between $75,000 and $105,000 (discounted).

11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated to be between $30 and $60 million in Year 5. The submission proposed a risk sharing agreement.

The PBAC noted that costings for the use of granulocyte colony-stimulating factors (g-CSF), as per the guidelines used in the clinical studies, were not included in financial estimates.

12. Recommendation and Reasons

The PBAC noted that, if listed as requested, a restriction similar to that for thalidomide would be appropriate.

The PBAC considered that where used instead of thalidomide, thalidomide is the appropriate comparator. However, lenalidomide may be used in patients who have previously failed thalidomide. In this patient population bortezomib is the appropriate comparator.

The PBAC noted that the basis of the comparison of lenalidomide versus thalidomide was the single arms of two direct randomised comparative trials with lenalidomide plus dexamethasone versus placebo plus dexamethasone and two cohort studies with thalidomide plus dexamethasone. The cohort studies with thalidomide were considered to be of very poor quality, and the scientific basis of the comparison was therefore of a much lower quality than is usually required to sustain a case for superiority.

The PBAC noted that there was no evidence of superiority of lenalidomide over thalidomide in progression-free survival, and considered a comparison of overall survival to be un-interpretable because of time biases (i.e. because the lenalidomide trials were conducted more recently). Other improvements in managing these patients may explain some or all of the claimed survival gains. On the data provided, even the case for the non-inferiority of lenalidomide and thalidomide is uncertain. Furthermore it cannot be anticipated that a

randomised trial directly comparing thalidomide plus dexamethasone with lenalidomide plus dexamethasone will be done.

Although the Committee considered that better evidence exists to support a comparison between lenalidomide and bortezomib, with both superior to dexamethasone alone, there remain uncertainties inherent in any indirect comparison.

Additionally, although the lenalidomide trials included subjects who had relapsed after thalidomide (42.5% in 009 and 33.9% in 010) or bortezomib (10.6% in trial 090 and 4.5% in trial 010), the impact of prior treatment with bortezomib or thalidomide remained uncertain.

With respect to comparative toxicity, no indirect comparison could be made between lenalidomide and thalidomide using a common comparator. Based on trial data it appeared the incidence of neuropathy is lower with lenalidomide compared to thalidomide. A comparison between lenalidomide and bortezomib indicates that the overall incidence of adverse events does not differ between them. However, the pattern of those events is different: lenalidomide treatment appears to be associated with significantly more neutropenia, insomnia and muscle cramps; bortezomib treatment appears to be associated with significantly more diarrhoea, nausea, peripheral neuropathy, vomiting, pyrexia, thrombocytopenia, cough, paraesthesia and bone pain.

Overall, the PBAC concluded there is great uncertainty about the relative clinical benefits of lenalidomide in comparison with either thalidomide or bortezomib.

The PBAC also considered there was uncertainty in the modelled economic evaluation. The inclusion of only the thalidomide naïve lenalidomide patients was inappropriate because the requested listing did not exclude patients who have received prior treatment with thalidomide. The total population of the lenalidomide trials was more appropriate for inclusion in the model as using only the thalidomide naïve patients would favour lenalidomide. There was also considerable uncertainty around the utility weights used and these utilities used did not incorporate the different safety profiles of lenalidomide and thalidomide.

The PBAC considered the incremental cost effectiveness ratios per life year gained and per QALY to be unacceptably high and uncertain.

The PBAC therefore rejected the application based on the quality of the data, the uncertainty of the clinical claim and the resulting unacceptably high and uncertain cost effectiveness ratios.

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 believes that lenalidomide is an important therapeutic option for the treatment of Multiple Myeloma patients in Australia. Celgene is therefore committed to working with the PBAC to address any areas of uncertainty and ensure that patients are able to access lenalidomide through the PBS.