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

1. Purpose of Application

To request a Section 100 (Highly Specialised Drugs Program) listing for the treatment of patients with relapsed/refractory multiple myeloma for whom thalidomide therapy has failed or in whom there is severe intolerance/toxicity to thalidomide.

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

At its March 2008 meeting, the PBAC rejected a submission to list lenalidomide for treatment of relapsed/refractory multiple myeloma based on the quality of the data, the uncertainty of the clinical claim and the resulting unacceptably high and uncertain cost-effectiveness ratios. (See also Public Summary Document for March 2008).

3. Registration Status

Lenalidomide was TGA registered 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 with multiple myeloma who has progressive disease, has received at least 1 prior therapy (other than thalidomide), has undergone or is ineligible for a primary stem cell transplant and who has experienced treatment failure after a trial of at least four (4) weeks of thalidomide at a dose of at least 100 mg daily.

If the dosing requirement for thalidomide cannot be met, the application must state the reasons why this criterion cannot be satisfied.

Thalidomide treatment failure is defined as:

1. confirmed disease progression during or after completion of thalidomide treatment; or
2. severe intolerance or toxicity unresponsive to clinically appropriate dose adjustment.

Progressive disease is defined as at least 1 of the following:

a. at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or
b. at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or
c. at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or

d. an increase in the size or number of lytic bone lesions (not including compression fractures); or
e. at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or
f. development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).

Severe intolerance due to thalidomide is defined as unacceptable somnolence or sedation interfering with activities of daily living. Toxicity from thalidomide is defined as peripheral neuropathy (Grade 2 or greater, interfering with function), drug-related seizures, serious Grade 3 or 4 drug-related dermatological reactions, such as Stevens-Johnson Syndrome, or other Grade 3 or 4 toxicity.

NOTE:
Patients receiving lenalidomide via the PBS must be registered in the RevAccess program.

For PBAC's view, see Recommendations 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. It is a rapidly progressing condition for which there is no cure. While existing treatments for newly diagnosed patients have the potential to delay disease progression and increase survival, eventually all patients will experience disease relapse, including those who have undergone a stem cell transplant. In some patients, their disease will fail to be controlled by those initial treatment options.

Lenalidomide would provide an alternative option for patients with relapsed or refractory multiple myeloma.

In the proposed treatment algorithm, patients will be treated with lenalidomide plus dexamethasone as third line therapy, after failing thalidomide and one other therapy.

6. Comparator

The submission nominated bortezomib, either as monotherapy or in combination with dexamethasone as the comparator. This is as previously advised by the PBAC and is appropriate.

7. Clinical Trials

New trial data were presented in the re-submission. The basis of the comparison with bortezomib was an indirect comparison of two lenalidomide plus dexamethasone and dexamethasone only trials (Study 009 and Study 010) compared with one bortezomib and dexamethasone trial (APEX) with dexamethasone as the common comparator, and two supportive bortezomib studies (Jagannath 2006, Kropff 2005). The previous submission did not present the two supportive bortezomib studies. The re-submission presented analyses including longer time to follow-up for the lenalidomide plus dexamethasone and dexamethasone only trials.

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

Trial ID / Author	Protocol title/ Publication title	Publication citation
Lenalidomide		
Randomised trials		
Study 009	Knight RD. Lenalidomide (Revlimid). A multicentre, randomized, parallel-group, double-blind, placebo-controlled study of CC-5013 plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma. September 2005.	Not published
Weber DM et al. (Study 009)	Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America.	N Engl J Med 2007; 357: 2133-2142.
Study 010	Knight RD. Lenalidomide (Revlimid). A multicentre, randomized, parallel-group, double-blind, placebo-controlled study of CC-5013 plus dexamethasone versus dexamethasone in previously treated subjects with multiple myeloma. September 2005.	Not published
Dimopoulos M, et al (Study 010)	Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma.	N Engl J Med 2007; 357: 2123-2132.
Wang M, et al (Study 009 and Study 010)	Lenalidomide plus dexamethasone is more effective than dexamethasone alone in patients with relapsed or refractory multiple myeloma regardless of prior thalidomide exposure.	Blood 2008; 112 (12): 4445-4451.
Bortezomib		
Randomised trial		
APEX		
Richardson PG et al. (2005)	Bortezomib or high dose dexamethasone for relapsed multiple myeloma.	N Engl J Med 2005; 352(24):2487-2498.
Richardson PG et al. (2007)	Extended follow-up of a phase 3 trial relapsed multiple myeloma: final time-to event results of the APEX trial.	Blood 2007; 110 (10): 3557-3560.
Richardson PG et al. (2007)	Safety and efficacy of bortezomib in high-risk and elderly patients with relapsed multiple myeloma	Br J Haematol. 2007; 137(5):429-35.
San-Miguel J-F et al. (2008)	Efficacy and safety of bortezomib in patients with renal impairment: results from the APEX phase 3 study.	Leukemia 2008; 22: 842–849.
Non-randomised studies		
Jagannath S et al (2006)	Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone.	Haematologica 2006; 91:929-934.

Trial ID / Author	Protocol title/ Publication title	Publication citation
Kropff M et al. (2005)	Bortezomib in combination with dexamethasone for relapsed multiple myeloma.	Leukemia Research 2005; 29:587-590.

8. Results of Trials

The key results are summarised in the tables below.

The primary outcome for the direct randomised trials was time to progression.

Results of time to progression across the direct randomised trials

	Study 009		Study 010		APEX	
	Len+Dex n = 177	**Dex** n = 176	**Len+Dex** n = 176	**Dex** n = 175	**Bort** n = 315	**Dex** n = 312
Median time of follow-up (months)	17	17	17	17	8.3	8.3
Median TTP (months)	11.1 (7.0, NE)	4.7 (3.9, 5.6)	11.3 (8.4, NE)	4.7 (4.6, 5.1)	6.2 (4.9, 6.9)	3.5 (2.8, 4.2)
HR (95% CI)	0.35 (0.27, 0.47)		0.35 (0.27, 0.46)		0.55 (0.44, 0.69)	
Log-rank test p-value	<0.001		<0.001		<0.001	

NE: not estimable, CI: confidence interval, HR: hazard ratio, Len: lenalidomide, Dex: dexamethasone, Bort: bortezomib.

In both lenalidomide trials, the median time to progression was significantly longer in the lenalidomide plus dexamethasone arm compared to the dexamethasone only arm. In the bortezomib trial, the median time to progression was significantly longer in the bortezomib arm compared to the dexamethasone only arm. The median time to follow-up in the lenalidomide plus dexamethasone trials (17 months) was longer than in the APEX trial (8.3 months). Furthermore, patients in the dexamethasone arm of Studies 009 and 010 were not allowed to cross-over until the time of un-blinding (median time to follow-up 17 months), while patients from the APEX trial were allowed to cross-over when they experienced disease progression. At the time of measurement, 44% of the dexamethasone patients in the APEX trial had crossed over to bortezomib treatment.

Taking into account the indirect nature of the comparison, the re-submission stated that there may be a suggestion, although not statistically demonstrated, that treatment with lenalidomide plus dexamethasone is associated with a longer time to progression than bortezomib in patients with relapsed/refractory multiple myeloma. The re-submission did not perform a proper indirect comparison of the two treatments, and there are differences in study design (moment when patients were allowed to cross-over to active treatment) and time of follow-up.

Overall survival was a secondary outcome for the direct randomised trials. The results for overall survival are presented below.

Overall survival

	Study 009 & Study 010		APEX	
	Len. + Dex. n = 353	**Dex.** n = 350	**Bort.** n = 315	**Dex.** n = 312
Median time of follow-up	41 months		22 months	
Dead n (%) **Censored** n (%)	147 (41.6) 206 (58.4)	173 (49.4) 177 (50.6)	NR	NR
OS (months) Median (95% CI) Mean St dev Min, Max	 34.4 (30.0, >41.8) 29.3 0.7 0.2, 41.8	 30.7 (25.6, 36.7) 26.6 0.9 0, 43.4	 29.8 (23.2, NE)	 23.7 (18.7, 29.1)
HR (95% CI)	0.77 (0.62, 0.96)		0.77 (0.61, 0.97)	
Log-rank test p-value	 0.02		 0.03	
Indirect comparison *len + dex vs. bort*	*1.00 (0.73, 1.38)*			

NR, not reported; CI, confidence interval; HR, hazard ratio; Len, lenalidomide; Dex, dexamethasone; Bort, bortezomib; NE, not estimable.

In both the lenalidomide and bortezomib trials, the investigational agent produced statistically significantly higher survival than dexamethasone alone.

The re-submission stated that comparison of these results across treatments suggests a numerical difference of 4.6 months in the median survival for patients treated with lenalidomide plus dexamethasone compared with bortezomib. The HR for the investigational agents relative to dexamethasone does not differ.

During the evaluation an indirect comparison was performed, using the HR from Studies 009 and 010 combined and the HR from the APEX trial. The HR for this indirect comparison is 1.00 (95%CI: 0.73 to 1.38). The clinical trial reports of Studies 009 and 010 did not present a definition of a clinical significant difference for overall survival. The 95% confidence intervals for the indirect comparison overlap with the HR for overall survival of 0.77 found in both Studies 009 and 010 combined and the APEX trial. The re-submission, as clarified in the Pre-Sub Committee Response, considered a HR of 0.77 to be statistically significant.

The PBAC noted the advice of the ESC that caution should be taken when interpreting this indirect comparison because:

a) the overall survival in the dexamethasone arm in the APEX trial was shorter than in Studies 009 and 010,

b) the ability to cross-over in both trials from the dexamethasone arm to the active treatment arm,

c) the time of follow-up was different between the lenalidomide plus dexamethasone trials and the bortezomib trial.

The re-submission presented updated toxicity data. Although the overall incidence of adverse events did not differ between lenalidomide plus dexamethasone and bortezomib, the pattern is different: lenalidomide plus dexamethasone treatment appears to be associated with more muscle cramps; bortezomib treatment appears to be associated with significantly more

diarrhoea, nausea, peripheral neuropathy, vomiting, pyrexia, thrombocytopenia, cough, paraesthesia and bone pain.

The incidence of grade 3 or 4 neutropenia (RD 19.4%) and insomnia (RD 2.1%) was significantly higher among lenalidomide plus dexamethasone treated patients, whereas the incidence of peripheral neuropathy (RD -7%), thrombocytopenia (RD -15.8%) and anorexia (RD -3.0%) was significantly higher among bortezomib treated patients.

Lenalidomide plus dexamethasone treatment was associated with higher incidences of deep-vein thrombosis (7.8% vs. 3.4%), venous thromboembolic events (13.0% vs. 4.0%) and pulmonary embolism (4.0% vs. 0.9%) than dexamethasone monotherapy. The publication for bortezomib does not report the incidence of deep vein thrombosis, venous thromboembolic events and pulmonary embolism associated with that treatment.

There were 12/343 (3.4%) reported cases of Grade 3/4 febrile neutropenia (FN) among the lenalidomide plus dexamethasone treated patients. The publications for the APEX trial do not report whether or not FN occurred, but both Jagannath 2006 and Kropff 2005 note no instances of that event.

9. Clinical Claim

The submission described lenalidomide plus dexamethasone as non-inferior in terms of comparative effectiveness and having a different safety profile compared to bortezomib.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The re-submission presented a cost analysis. The equi-effective doses were estimated as lenalidomide 21.9 mg for 21 days per 28 day cycle over 6.84 months and bortezomib 1.3 mg/m^2 of body surface area on day 1, 2, 8 and 11 of 21 day cycles over 4.39 months (6.37 cycles).

Lenalidomide is co-administered with dexamethasone at 40 mg on days 1 to 4, 9 to 12 and 17 to 20 of each 28 day cycle for the first four cycles of therapy. From cycle 5 onwards, the schedule for the dexamethasone dose was reduced to days 1 to 4 of every 28 day cycle for 6.84 months.

The re-submission assumed for the cost-analysis that dexamethasone is co-administered in 90% of bortezomib patients at a dose of 40 mg on the days that bortezomib was infused, for 4.39 months.

The equi-effective doses presented in the re-submission for the cost analysis were not the doses used in the clinical trials.

The re-submission included the following costs in the cost-analysis:

1) cost of drug treatment (lenalidomide, bortezomib and dexamethasone),
2) costs for the treatment of Grade 3/4 adverse events which were significantly different between lenalidomide plus dexamethasone versus bortezomib treatment, and
3) the cost of administration of bortezomib infusion.

The re-submission did not use the ITT population for calculating the response rate. During the evaluation response rates using the ITT population were used to calculate the average number of cycles.

11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated in the re-submission to be less than $10 million in Year 5, compared with between $30-60 million in the previous submission.

The likely number of patients per year using lenalidomide was estimated in the re-submission to be less than 10,000 in Year 5. This number was reduced from the previous submission.

12. Recommendation and Reasons

The PBAC recommended the listing of lenalidomide for the treatment of patients with relapsed/ refractory multiple myeloma for whom thalidomide therapy has failed or in whom there is severe intolerance/ toxicity to thalidomide. Listing was recommended on a cost minimisation basis with bortezomib with the equi-effective doses to be based on 6 cycles of bortezomib, in line with the submission's approach.

The Committee accepted the claim of non-inferiority of lenalidomide plus dexamethasone in terms of comparative effectiveness compared to bortezomib based on the indirect comparison. The Committee noted that overall survival may possibly favour lenalidomide with dexamethasone, however there is uncertainty due to the indirect comparison, and the differences in the trials used for comparison.

The PBAC accepted that lenalidomide used in combination with dexamethasone has a different side effect profile from bortezomib. It was observed that the incidence of grade 3 or 4 neutropenia was significantly higher with lenalidomide plus dexamethasone treated patients, and the incidence of peripheral neuropathy and thrombocytopenia was significantly higher among bortezomib treated patients.

The Committee considered one of the key uncertainties in the pre-modelling studies was the average number of bortezomib cycles assumed. The submission assumed 6.37 cycles, however it was agreed that this was likely an overestimate as the ITT population from the APEX trial was not used and the assumptions in the methodology overestimated the number of cycles for partial responders and non-responders. The PBAC supported using 6 cycles of bortezomib, which was calculated using the ITT population in the APEX trial with the same methodology as presented in the submission.

The other key area of uncertainty in the pre-modelling studies noted by the Committee was the modification of the response rate to bortezomib, adjusting for response to combination therapy with dexamethasone. The PBAC agreed that it was reasonable to adjust the response to encompass combination with dexamethasone as this would more closely align to the PBS use of bortezomib and accepted the factor of 1.2 presented in the submission.

The PBAC considered that combination therapy of lenalidomide with bortezomib should not be allowed on the PBS and noted the sponsor's agreement to this in the pre-Sub-Committee response. The Committee advised that the restriction should exclude the combination treatment of lenalidomide with bortezomib. The PBAC also advised that patients receiving

lenalidomide prior to PBS listing will not be automatically grandfathered. Grandfathering criteria are to be developed. The Committee also advised that the listing of lenalidomide should be administered by written authority applications in a similar way to bortezomib.

Recommendation

LENALIDOMIDE, capsule, 5 mg, 10 mg, 15 mg and 25 mg

Restriction:

Section 100 (Highly Specialised Drugs Program)

NOTE:

Any queries concerning the arrangements to prescribe lenalidomide may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Prescribing information (including Authority Application forms) is available on the Medicare Australia website at www.medicareaustralia.gov.au.

Any queries concerning patients who are enrolled on the Lenalidomide Compassionate program may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). These patients must demonstrate they met initial criteria prior to commencing treatment on the compassionate program and also demonstrate they do not have progressive disease. Baseline and current pathology reports must be submitted with the initial application.

Applications for authority to prescribe lenalidomide should be forwarded to:

Medicare Australia
Prior Written Approval of Specialised Drugs
Reply Paid 9826
GPO Box 9826
HOBART TAS 7001

Public and private hospital authority required

Initial PBS-subsidised treatment, as monotherapy or in combination with dexamethasone, of multiple myeloma in a patient who has progressive disease, who has received at least 1 prior therapy (other than thalidomide), who has undergone or is ineligible for a primary stem cell transplant and who has experienced treatment failure after a trial of at least four (4) weeks of thalidomide at a dose of at least 100 mg daily.

If the dosing requirement for thalidomide cannot be met, the application must state the reasons why this criterion cannot be satisfied.

Thalidomide treatment failure is defined as:

1. confirmed disease progression during or within 6 months of discontinuing thalidomide treatment; or
2. severe intolerance or toxicity unresponsive to clinically appropriate dose adjustment.

Any queries concerning additional details about treatment failure may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Progressive disease is defined as at least 1 of the following:

a. at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or
b. at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or
c. at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or
d. an increase in the size or number of lytic bone lesions (not including compression fractures); or
e. at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or
f. development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).

Severe intolerance due to thalidomide is defined as unacceptable somnolence or sedation interfering with activities of daily living. Toxicity from thalidomide is defined as peripheral neuropathy (Grade 2 or greater, interfering with function), drug-related seizures, serious Grade 3 or 4 drug-related dermatological reactions, such as Stevens-Johnson Syndrome, or other Grade 3 or 4 toxicity.

Lenalidomide will only be subsidised for patients with multiple myeloma who are not receiving concomitant PBS-subsidised bortezomib.

The authority application must be made in writing and must include:
(1) a completed authority prescription form; and
(2) a completed Multiple Myeloma Authority Application – Supporting Information Form, which includes details of prior treatments including name(s) of drug(s) and date of most recent treatment cycle and record of prior stem cell transplant or ineligibility for prior stem cell transplant; details of thalidomide treatment failure; and details of the basis of the diagnosis of progressive disease.

To enable confirmation by Medicare Australia of eligibility, current diagnostic reports of the following are required:

(a) the level of serum monoclonal protein; and
(b) if Bence-Jones proteinuria is present, the results of 24-hour urinary light chain M protein excretion..
If neither serum M protein or urine Bence-Jones protein are present in measurable quantities, additional diagnostic reports are required, including:
(c) bone marrow aspirate and trephine; and
(d) if present, the size and location of lytic bone lesions (not including compression fractures); or
(e) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or
(f) if present, the level of hypercalcaemia, corrected for albumin concentration; or
(g) if present, the serum free light chain levels..
Results for (a) and (b) should be provided for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, (c) must be provided and if relevant (d), (e) or (f). In patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, (g) must be provided. Where 1 or more results cannot be provided, the application must state the reason(s) these cannot be provided; and
(3) duration of thalidomide and daily dose prescribed; and
(4) a signed patient acknowledgement.

NOTE:
Patients receiving lenalidomide via the PBS must be registered in the RevAccess program.

Public and private hospital authority required
Continuing PBS-subsidised treatment, as monotherapy or in combination with dexamethasone, of multiple myeloma in a patient who has previously been issued with an authority prescription for lenalidomide and who does not have progressive disease.

Progressive disease is defined as at least 1 of the following:

a. at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or
b. at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or
c. at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or
d. an increase in the size or number of lytic bone lesions (not including compression fractures); or
e. at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or

f. development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).

Authority applications for continuing treatment may be made by telephone to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Pack size: 21

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 welcomes the recommendation of the PBAC for the listing of Revlimid in relapsed/refractory multiple myeloma. The Sponsor considers that the recent approval for the same indication by the National Institute of Clinical Excellence in England and Wales further supports the position adopted by the PBAC.