PUBLIC SUMMARY DOCUMENT
Product: Lenalidomide, capsules, 5 mg and 10 mg, Revlimid®
Sponsor: Celgene Pty Ltd
Date of PBAC Consideration: March 2011

1. Purpose of Application

The submission sought an extension to the Section 100 (Highly Specialised Drug) Public and Private Authority Required listing to include initial and continuing treatment of a patient with myelodysplastic syndrome (MDS), defined as low or intermediate-1, who has a 5q cytogenetic abnormality and who is red blood cell transfusion dependent.

2. Background

This drug had not previously been considered by the PBAC for this indication.

3. Registration Status

An extension to the TGA registration for lenalidomide was granted on 15 April 2010 to include the treatment of patients with transfusion-dependent anaemia due to low or imtermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Lenalidomide was TGA registered on 20 December 2007 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 (Highly Specialised Drug)
Public and Private Hospital Authority Required
Initial treatment for a period of up to 16 weeks of a patient with:

- MDS classified as low risk or Intermediate-1 according to the International Prognostic Scoring System (IPSS); and
- Who has a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities; and
- Who is red blood cell transfusion dependent.

Classification of a patient as low risk requires a score of 0 on the IPSS, achieved with the following combination: < 5% marrow blasts with good karyotypic status (normal, -Y alone, -5q alone, -20q alone), and 0/1 cytopenias.

Classification of a patient as Intermediate-1 requires a score of 0.5 to 1 on the IPSS, achieved with the following possible combinations:

1. 5%-10% marrow blasts with good karyotypic status (normal, -Y alone, -5q alone, -20q alone), and 0/1 cytopenias; OR
2. < 5% marrow blasts with intermediate karyotypic status (other abnormalities), and 0/1 cytopenias; OR
3. < 5% marrow blasts with good karyotypic status (normal, -Y alone, -5q alone, -20q alone), and 2/3 cytopenias; OR
4. < 5% marrow blasts with intermediate karyotypic status (other abnormalities) and 2/3 cytopenias; OR

5. 5%-10% marrow blasts with intermediate karyotypic status (other abnormalities), and 0/1 cytopenias; OR
6. 5%-10% marrow blasts with good karyotypic status (normal, -Y alone, -5q alone, -20q alone), and 2/3 cytopenias; OR
7. < 5% marrow blasts with poor karyotypic status (complex, > 3 abnormalities), and 0/1 cytopenias.

Public and Private Hospital Authority Required
Continuing treatment of a patient with:
MDS classified as low risk or Intermediate-1 according to the International Prognostic Scoring System (IPSS); and
Who has a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities; and
Who is red blood cell transfusion dependent;
Who has been previously issued with an authority prescription for lenalidomide and who achieved at least a 50% reduction in their red blood cell transfusion requirements during that treatment and remained free from disease progression.

Note:
Patients receiving lenalidomide under the PBS listing must be registered in the i-access™ risk management program.

The requested maximum quantity is one pack of 21 capsules with two repeats, allowing for three months of treatment.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

The myelodysplastic syndromes (MDS) are a group of disorders of haematopoiesis (formation of blood cellular components), which include refractory anaemia, chronic myelomonocytic leukaemia (CMML), acute myeloid leukaemia (AML) and a specific subtype characterised by the presence of a deletion of the 5q chromosome. Presence of a 5q deletion occurs in approximately 10% of patients with MDS. The 5q deletion subtype is typically associated with a better prognosis for survival and freedom from progression to AML than occurs in patients without a 5q deletion.

The incidence of MDS is highest among older persons, with the median age of diagnosis being in the range of 65 to 70 years. There are currently no curative options available for most patients with MDS although a small percentage of younger and fitter patients may achieve long-term disease control through allogeneic transplantation. Almost all patients with MDS will receive background supportive therapy. Active therapies will be used in patients at higher risk of transforming to leukaemia.

The submission proposed that the place in therapy of lenalidomide was to provide an alternative treatment option to best supportive care for patients who are unable or not suitable to be treated with active chemotherapy/stem cell transplantation.

6. Comparator

The submission nominated best supported care (BSC) comprising red blood cell transfusions, treatment with granulocyte colony stimulating factor, blood forming and iron chelation therapy as the comparator, which was considered appropriate by the PBAC.

7. Clinical Trials

The submission presented one randomised trial MDS-004, comparing 10 mg or 5 mg lenalidomide once daily for 21 days in every 28 day cycle with best supported care in patients with transfusion dependent low risk/INT-1 del(5q) myelodysplastic syndrome.

The key trials published at the time of submission are shown in the table below:

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trial		
MDS-004		
Fenaux, P. et al	Safety of lenalidomide (LEN) from a randomized phase III trial (MDS-004) in low-/int-1-risk myelodysplastic syndromes (MDS) with a del(5q) abnormality.	J Clin Oncol. 2010; 28:15s: 6598.
Fenaux, P. et al	4027 Prognostic Factors of Long-Term Outcomes In Low- or Int-1-Risk MDS with del5q Treated with Lenalidomide (LEN): Results From a Randomized Phase 3 Trial (MDS-004).	Abstract 52nd American Society Hematology Meeting, December 2010.
Supplementary non randomised trial		
CC-5013-MDS-003		
List, A. et al	Lenalidomide in the myelodysplastic syndrome with chromosome del(5q).	New England Journal of Medicine 2006; 355(14): 1456-1465
Sekeres, M. A. et al	Relationship of treatment-related cytopenias and response to lenalidomide in patients with lower-risk myelodysplastic syndromes.	Journal of Clinical Oncology 2008; 26(36): 5943-5949

8. Results of Trials

The primary outcome of MDS-004 was the proportion of patients achieving red blood cell (RBC) transfusion independence for ≥182 days (6 months) in the MITT (modified intention to treat) population measured at 52 weeks. The secondary outcome of the International Working Group for MDS (IWG) criteria was defined as transfusion independence ≥56 days.

The results for the primary outcome and key secondary outcome are summarised below:

The ITT (intention to treat) and MITT results from both the primary (transfusion independence for ≥ 182 days) and key secondary outcomes (IWG criteria transfusion dependence ≥56 days) demonstrated that patients treated with lenalidomide had a statistically significantly greater chance of becoming transfusion independent than placebo treated patients.

The PBAC noted that a clinically meaningful change in patients' HRQoL (health related quality of life) was observed after 24 weeks of treatment with lenalidomide and a worsening in placebo patients. However, the results were confounded due to loss to follow up.

No differences were found in either progression to acute myeloid leukaemia (AML) or overall survival at the date of primary analysis. Limited long term data on overall survival was provided by the submission and rates were not provided for placebo due to cross-over.

Serious adverse events were frequent with lenalidomide treatment with 94% of subjects in the 10 mg arm having at least one Grade 3/4 adverse event. Lenalidomide was associated with statistically significant higher rates of neutropenia (75.4% in the lenalidomide 10 mg group versus 14.9% in the placebo group); thrombocytopenia (40.6% in the lenalidomide 10 mg group versus 1.5% in the placebo group); leucopenia (not otherwise specified) (8.7% in the lenalidomide 10 mg group versus 0% in the placebo group); and non-statistically significant higher rates of vascular disorders: deep vein thrombosis (5.8% in the lenalidomide 10 mg group versus 1.5% in the placebo group).

9. Clinical Claim

The submission described lenalidomide as superior in terms of comparative effectiveness and associated with more toxicity over best supported care, which was considered reasonable based on the supporting data.

10. Economic Analysis

The submission presented a stepped economic evaluation, based on the pivotal trial.

The model was a decision analytic model which compared the use of lenalidomide (plus BSC) with BSC alone for the treatment of patients with transfusion dependent low risk/INT-1 del(5q) MDS over a time horizon of 12 months. Costs of treating Grade 3/4 adverse events associated with lenalidomide treatment were estimated in the model. The main drivers of the model were the proportion of patients achieving transfusion independence and the cost of lenalidomide. Utilities in the model were assigned for transfusion dependence and independence, with no adjustment for a reduction of 50% RBC transfusion requirement. These patients were assigned transfusion dependent utilities.

The re-specified base case incremental cost per extra QALY gained was estimated to be between $45,000 – $75,000.

The result of the univariate sensitivity analyses indicated that the model was highly sensitive to a number of parameters including the price of lenalidomide, the pack usage of lenalidomide and the utility values used in the model.

The model was also highly sensitive to the assumed use of iron chelation therapy.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the total net cost to the PBS to be less than $10 million per year in Year five after listing.

12. Recommendation and Reasons

The PBAC agreed that the appropriate comparator was best supportive care.

The submission presented one randomised trial MDS-004, comparing 10mg or 5mg lenalidomide once daily for 21 days in every 28 day cycle with best supportive care in patients with transfusion dependent low risk/INT-1 del(5q) myelodysplastic syndrome. The PBAC agreed that the ITT and MITT (modified intention to treat) results from both the primary (transfusion independence for ≥ 182 days) and key secondary outcomes (IWG criteria transfusion dependence ≥56 days) demonstrate that patients treated with lenalidomide had a statistically significantly greater chance of becoming transfusion independent than placebo treated patients. The PBAC noted that a clinically meaningful change in patients' HRQoL was observed after 24 weeks of treatment with lenalidomide and a worsening in placebo patients. However, the results were confounded due to loss to follow up.

The submission claimed that lenalidomide is superior in terms of comparative effectiveness and associated with more toxicity over best supported care. The PBAC considered that for the primary outcome of transfusion independence this is reasonable based on the supporting data.

The PBAC noted that the requested restriction did not provide a definition of transfusion dependence. The PBAC considered that a definition could be based on the criteria used in the trial or alternatively "at least 8 units of RBC in last 6 months", which is similar to the description of transfusion dependence described by the clinician at the sponsor's Hearing. However, this may still be difficult for Medicare Australia to implement, as there is some difficulty in accurately recording the information. This was reflected in the exclusion of a significant minority of patients from the mITT because transfusion data were not able to be verified. There is also potential for manipulation of transfusion regimens to artificially meet any arbitrary definition within a certain time period. The PBAC also noted that the restriction specified a 50% reduction in transfusions for continuing therapy implying that reduced transfusion dependence is a relevant state. However, this was not modelled in the modelled economic evaluation. The 50% reduction was consistent with the 16 week continuation criteria in trial and whilst this may be a reasonable clinical indicator for ongoing use, it would be difficult for Medicare Australia to administer. It is also possible that at any given time, the requirement for a red cell transfusion would not exclusively reflect failure of lenalidomide, but rather that an intercurrent and correctable medical issue had arisen which required transfusion. The PBAC considered that the requirement of a 50% transfusion reduction may be best handled by inclusion of this in the economic model or by a risk share arrangement.

The submission presented a stepped economic evaluation, based on the pivotal trial.
The PBAC noted that the model is highly sensitive to a number of parameters including the price of lenalidomide, the pack usage of lenalidomide and the utility values used in the model. The model is also highly sensitive to the assumed use of iron chelation therapy. The PBAC did not consider that the assumed 51% rate of use prior to transfusion independence, reducing to 19% for transfusion independence, is likely to be an overestimate if the truly-transfusion dependent low risk myelodysplasia population alone was included.

The PBAC noted that the cost of deferasirox was incorrect and the costs of weekly blood tests and reviews for the first two months were omitted from the lenalidomide arm. The base case was re-specified and estimated to be in the range $45,000 – $75,000 per QALY
but was considered to be very uncertain, due to various concerns with the assumptions made in the model, such as:

- no inclusion of transition to AML or death;
- no modelling of the continuation rule, which required 50% reduction in transfusions;
- uncertainty in relation to the likely numbers of packs used per patient; and
- use of utility values taken from literature which reported the greatest difference in values for transfusion independent and dependent patients.

The PBAC noted that no QoL parameters were reported in the clinical trials presented that could be converted to QALY weights. Of the two available literature studies (Szende et al 2010 and Buckstein et al 2009), the model used the values from Szende, which were more favourable to lenalidomide. Sensitivity analyses using Buckstein increased the ICER from $45,000 – $75,000in the respecified base case to $75,000 – $105,000. The PBAC noted the Szende study, which included three health states, transfusion independence, reduced transfusion burden and transfusion dependence. The vignette for reduced transfusion burden was not included in the published study. The PBAC considered that this intermediary state of reduced transfusion dependence may have been a useful health state to be included in the model for those patients eligible to continue treatment but not reaching transfusion independence. The PBAC noted that by not including this health state there was some potential for the utility gain to be overstated (given that patients not achieving transfusion independence were assigned the utility for transfusion dependence) particularly as the vignettes for the transfusion independent , reduced transfusion burden state and dependent state differed substantially on all aspects of the health state, for example social and role function and anxiety, and may not be truly representative of those states in myelodysplasia patients.

The PBAC noted that the definition of transfusion independence used in the model is based on 56 days (secondary outcome) rather than 182 days (primary outcome). However, 182 days may be a more appropriate outcome to extrapolate to one year.

The PBAC considered that although lenalidomide was an effective drug, neither the restriction nor the model adequately reflected the likely place in clinical practice.

The PBAC therefore rejected the submission on the basis of a high and uncertain 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

Celgene will continue to work with the PBAC to achieve a positive recommendation for lenalidomide for patients with myelodysplastic syndrome (MDS), defined as low or intermediate-1, who have a 5q cytogenetic abnormality and who are red blood cell transfusion dependent.