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

## 1. Purpose of Application

The re-submission sought to extend the Section 100 (Highly Specialised Drugs Program) Public and Private Hospital Authority Required listing to include the initial and continuing treatment of patients with myelodysplastic syndrome (MDS) defined as low or immediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality that are transfusion-dependent.

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 the March 2011 meeting, the PBAC rejected a submission to list lenalidomide for treatment of MDS on the basis of a high and uncertain cost-effectiveness ratio. The PBAC considered that although lenalidomide was an effective drug for use in MDS, neither the proposed restriction nor the model adequately reflected the likely place in clinical practice.

A copy of the Public Summary Document from the March 2011 meeting is available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-lenalidomidel-march11

## 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 Drugs Program)
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.

Classification of a patient as transfusion dependent requires that they have received at least eight units of red blood cells over the most recent six month period prior to requesting access to lenalidomide on the PBS.

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 has been previously issued with an authority prescription for lenalidomide and who has achieved a clinically relevant 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.

*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

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 consisting of red blood cell (RBC) and platelet transfusions, antibiotics, growth factor support and iron chelating therapy. Active therapies will also be used in patients at higher risk of transforming to leukaemia.

The submission proposed that the place in therapy of lenalidomide is as 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 placebo (best supportive care) as the main comparator which the PBAC had previously agreed to be appropriate.

## 7. Clinical Trials

No new data were presented in the re-submission. Publication details and results of the studies presented in the March 2011 submission have been previously reported in the March 2011 PSD.

## 8. Summary of Submission

The submission provided the following to address the PBAC's concerns from the March 2011 meeting:

- Changes to the proposed restriction for lenalidomide, in particular inclusion of a definition for transfusion dependence of at least eight units of red blood cells in the last 6 months and exclusion of the requirement for access to continuing therapy;
- A revised for use of lenalidomide in MDS; and
- Updated estimates of the financial impact to government of listing lenalidomide at the revised price.

## 9. Clinical Claim

The March 2011 submission described lenalidomide as superior in terms of comparative effectiveness and associated with more toxicity over best supportive care. This was considered reasonable by the PBAC based on the supporting data.

## 10. Economic Analysis

The basis and structure of the economic model for lenalidomide were unchanged from those considered by the PBAC for the March 2011 meeting. The revised price resulted in a reduction in the base cost per quality adjusted life year (QALY) gained, compared with the March 2011 submission. The ICER was reduced, but remained in the range of $45,000-$75,000.

The updated economic analysis included:

- Additional haematologist visits and blood tests;
- Corrections to the cost of deferasirox;
- A price revision.

The ICER was increased (within the same range) when Buckstein 2009 utilities were used in the sensitivity analysis.

The re-submission claimed that while not modelled separately within the economic evaluation, the effects of the continuation rule were reflected in the average number of packs consumed. Moreover, all efficacy analyses used in the economic evaluation were based on the double-blind period of the trial, and therefore similarly reflected the impact of patients having discontinued treatment at 16 weeks due to lack of response.

*For PBAC's views, see Recommendation and Reasons.*

## 11. Estimated PBS Usage and Financial Implications

The financial implications of expanding the current listing for lenalidomide to include -5q MDS were revised from the March 2011 PBAC submission to incorporate:

- An increase in the proportion of patients with -5q MDS;
- An adjusted price of deferasirox; and
- A revised price for the 5mg and 10mg strengths of lenalidomide used in MDS.

The likely number of patients per year was estimated in the re-submission to be less than 10,000 in Year 5 at an estimated net cost per year to the PBS of less than $10 million in Year 5. The revised estimates were greater than in the March 2011 submission.

*For PBAC's view, see Recommendation and Reasons.*

## 12. Recommendation and Reasons

The PBAC noted that no new data were presented in the re-submission but the following changes had been made in the re-submission: a revised price, a revised restriction with transfusion dependence defined as 8 or more units in 6 months, the number of patients increased to 15% of all MDS patients and the ICER recalculated using the Buckstein utilities at the price proposed.

The PBAC considered that as the resubmission did not account for ongoing long-term use in partial responders in the economic model, inclusion of continuing treatment criteria would be necessary. The PBAC proposed that the initial authority could be written but a telephone authority may be acceptable at 4 monthly intervals. The PBAC agreed with the definition of transfusion dependence which requires patients to have received at least 8 units of red cells over the most recent 6 months prior to requesting access to lenalidomide on the PBS, but considered that the following wording should be added "*and would be expected to continue this requirement without lenalidomide treatment*."

The PBAC noted that the percentage of patients expected to receive lenalidomide for low risk /INT-1-5q MDS had been increased in the re-submission from 10% to 15 % which the PBAC considered was an overestimate and agreed that 10% of patients would be more likely.

The PBAC noted that the re-submission recalculated the ICER using the Szende utilities at the revised price proposed which was estimated to be between $45,000 and $75,000 per QALY gained (lower than in March 2011). Using the Buckstein utilities it was estimated to be higher within the same range per QALY gained (compared with between $70,000 and $105,000 in March 2011). The PBAC recalled that in the March 2011 submission the Szende study did include utilities for reduced transfusion burden and that by not including this health state in the model there was some potential for the utility gain to be either over- or understated (given that patients not achieving transfusion independence were assigned the

utility for transfusion dependence). The PBAC considered that by using the same utilities to recalculate the ICER but at the reduced price, the estimated ICER was still high and uncertain. The PBAC considered that a price reduction would be necessary to account for the uncertainty in the economic model because of the lack of certainty with the utilities.

The PBAC further noted that there was no modelling of a continuation rule in the economic model, in which there is a 50% reduction in transfusions, and therefore the risk of non cost-effective continuation of lenalidomide long term had not been dealt with in economic model. A continuation rule would be necessary to deal with this uncertainty and treatment beyond 1 year would require complete or near transfusion independence. The PBAC considered that doctors would need to affirm that transfusion requirements have reduced by 50% at least after 4 and 8 months.

The PBAC therefore rejected the submission on the basis of a high and uncertain cost-effectiveness ratio. The PBAC considered that a major submission would be required to address the uncertainties in the economic model.

The PBAC noted the consumer comments received in its consideration of lenalidomide.

***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 disagrees with the decision and sympathises with patients that will not be able to access Revlimid for MDS.