

## 6.02 LENALIDOMIDE, ORAL CAPSULES, 5 MG, 10 MG, 15 MG, 25 MG, REVLIMID®, CELGENE PTY LTD.

### 1 Purpose of Application

- 1.1 The submission requested Section 100 Highly Specialised Drug, Authority Required listing for the treatment of relapsed and/or refractory mantle cell lymphoma in patients who are unable to tolerate intensive chemotherapy.

The PBAC noted that the specified group of patients for whom listing was sought immediately defines a cohort with a very short life expectancy.

### 2 Requested listing

- 2.1 Lenalidomide was proposed for the treatment of relapsed and/or refractory mantle cell lymphoma in adult patients. Specifically, the requested listing was for use following at least one prior first-line therapy in patients who are unable to tolerate intensive chemotherapy or stem-cell transplantation. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

| Name, Restriction, Manner of administration and form  | Max. Qty   | No. of Rpts | Dispensed Price for Max. Qty (effective price) <sup>ab</sup>     |  | Proprietary Name and Manufacturer |
|---|--|-------------|--|--|-----------------------------------|
|   |  |             | Public   | Private  |                                   |
| LENALIDOMIDE<br>Oral capsule 5 mg<br>Oral capsule 10 mg<br>Oral capsule 15 mg<br>Oral capsule 25 mg | 21   | 0           | \$ [REDACTED]<br>\$ [REDACTED]<br>\$ [REDACTED]<br>\$ [REDACTED] | \$ [REDACTED]<br>\$ [REDACTED]<br>\$ [REDACTED]<br>\$ [REDACTED] | Revlimid®<br>Celgene Pty Ltd      |
| Episodicity:  | Chronic  |             |  |  |                                   |
| Severity:   | <del>N/A</del> Relapsed and/or refractory  |             |  |  |                                   |
| Condition:  | Mantle cell lymphoma   |             |  |  |                                   |
| PBS Indication:   | Relapsed and/or refractory mantle cell lymphoma  |             |  |  |                                   |
| Restriction:  | Authority Required – In Writing  |             |  |  |                                   |
| Phase of treatment:   | Initial or continuing PBS-subsidised treatment   |             |  |  |                                   |
| Treatment criteria:   | Must be treated by a haematologist or oncologist   |             |  |  |                                   |
| Clinical criteria:  | <p><u>Initial:</u><br/> <del>Patient must have mantle cell lymphoma</del><br/> AND<br/> <del>Patient must have received at least one prior therapy for this indication</del><br/> AND<br/> <del>Patient must have progressive disease after at least one prior therapy,</del><br/> AND<br/> <del>Patient must be ineligible for intensive chemotherapy;</del><br/> OR<br/> <del>Patient must be ineligible for stem cell transplant at time of application,</del><br/> AND<br/> Patient must be registered in the <i>i-access</i> risk management program.</p> <p><u>Continuing:</u></p> |             |  |  |                                   |

|                 |  |
|-----------------|--|
|                 | <p>Patient must have received an initial authority prescription for <i>this drug</i> lenalidomide for this <i>condition</i> indication,<br/> AND<br/> <del>Patient must not have demonstrated progressive disease at the time of application,</del><br/> <i>Patient must not have progressive disease,</i><br/> AND<br/> Patient must be registered in the i-access risk management program.</p> |
| <b>Cautions</b> | <i>This is a category X drug and must not be given to pregnant women. Pregnancy must be avoided during treatment and for at least 3 months following cessation of therapy.</i>   |

<sup>a</sup> The submission stated that the effective prices reflected the effective prices per 1 April 2016 for progressive multiple myeloma. However, there were some small discrepancies which were updated during evaluation.

<sup>b</sup> These prices are as proposed in the submission. The sponsor, in their pre-PBAC response, proposed a ■% discount to the effective AEMP in the submission.

- 2.2 The submission presented a cost-effectiveness analysis of lenalidomide monotherapy compared with a weighted mix of fludarabine, gemcitabine, chlorambucil, cytarabine or rituximab monotherapy. The evidence provided in the submission was not consistent with the requested restriction. In the clinical trial lenalidomide was provided as monotherapy, while the restriction proposed by the submission and the approved TGA indication do not restrict lenalidomide use to monotherapy. The PSCR noted that the sponsor's preference was for the restriction not to specify use as monotherapy only, but that the sponsor would support such a restriction if the PBAC was of the view that it was necessary.
- 2.3 The PBAC noted that the sponsor in their pre-PBAC response offered a ■% discount to the effective AEMP proposed in the submission.

### 3 Background

- 3.1 Lenalidomide was TGA registered on 4 March 2016 for the treatment of patients with relapsed and/or refractory mantle cell lymphoma.
- 3.2 Lenalidomide is currently listed on the PBS for use in combination therapy with dexamethasone in patients with progressive multiple myeloma, and myelodysplastic syndrome. In November 2015, the PBAC recommended listing of lenalidomide for the treatment of patients with newly diagnosed multiple myeloma. At the time of evaluation, listing had not proceeded.

### 4 Clinical place for the proposed therapy

- 4.1 Mantle cell lymphoma is a rare and aggressive type of non-Hodgkin lymphoma and is characterised by the overexpression of cyclin D1, leading to cell cycle deregulation and proliferation of B-cells in the mantle zone of lymph nodes. In the proposed clinical algorithm, lenalidomide monotherapy is to be used in adult patients with relapsed and/or refractory mantle cell lymphoma. Patients must be enrolled in the i-access<sup>®</sup> program, and must have had at least one prior therapy and be unfit for intensive immune-chemotherapy treatment.

- 4.2 The ESC noted that lenalidomide would provide an additional line of therapy for elderly/frail patients, but overall considered that the current management of relapsed/refractory mantle cell lymphoma in Australian practice was not well described in the submission. The ESC considered that this made it difficult to determine the place in therapy of lenalidomide in the proposed PBS population.
- 4.3 The PBAC recognised that there is a need for a treatment option that induces a high response rate with minimal toxicity for patients with relapsed/refractory MCL, who are unsuitable for chemotherapy. The Committee considered that the appropriate clinical place for lenalidomide if listed would be in the management of this cohort of patients for whom there are currently no PBS subsidised treatments.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **5 Comparator**

- 5.1 The submission nominated a weighted mix of chemotherapy regimens as the comparator. The submission considered that identification of a single main comparator was neither possible nor appropriate given current treatment practices.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from health care professionals (3) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits with lenalidomide treatment including a prolonged response and improved quality of life in approximately 20% of treated patients, and that lenalidomide was a well-tolerated therapeutic alternative for a small patient population with an urgent clinical need.
- 6.3 The PBAC noted the advice received from the Australian Leukaemia and Lymphoma Group clarifying the current treatment algorithm for patients with relapsed and/or refractory mantle cell lymphoma, the treatment options available, clinician preferred treatment options, and the likely use of lenalidomide in this setting. The PBAC specifically noted the advice that the use of lenalidomide would be restricted to a small cohort of very frail patients with a very short life expectancy and that it would be unlikely to displace any current PBS subsidised treatments. The PBAC also noted that management of mantle cell lymphoma in Australia is currently evolving.

## Clinical trials

6.4 The submission was based on MCL-002, an open-label randomised trial (2:1) that compared lenalidomide monotherapy with the investigator’s choice of therapy (n = 254).

6.5 Details of the trial presented in the submission are provided in the table below.

**Table 1: Trial and associated reports presented in the submission**

| Trial ID                       | Protocol title/ Publication title   | Publication citation                              |
|--------------------------------|---|---|
| <b>Direct randomised trial</b> |   |   |
| MCL-002                        | A Phase II multi-centre, randomised, open-label study to determine the efficacy of lenalidomide (Revlimid®) versus investigator’s choice in patients with relapsed or refractory mantle cell lymphoma.<br><br>Trneny M, Lamy T, Walewski J, et al. Lenalidomide versus investigator’s choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multi-centre trial. | March 2014<br><br>Lancet Oncol. 2016; 17:319-331. |

Source: Table B.3, p25 of the submission

6.6 The key features of the direct randomised trial are summarised in the table below.

**Table 2: Key features of the included evidence**

| Trial  | N   | Design/ duration                    | Risk of bias | Patient population   | Outcome(s)                            | Use in modelled evaluation |
|--|-----|-------------------------------------|--------------|--|---------------------------------------|----------------------------|
| <b>Lenalidomide vs investigator’s choice</b> |     |                                     |              |  |                                       |                            |
| MCL-002                                      | 254 | R, MC, OL, 15.9 months <sup>a</sup> | High         | Relapsed/refractory MCL, not suitable for intensive chemotherapy | PFS, OS, ORR, safety, quality of life | Yes                        |

Source: compiled during the evaluation

MC = multi-centre; MCL = mantle cell lymphoma; OL = open-label; ORR = overall response rate; OS = overall survival; PFS = progression free survival; R = randomised

<sup>a</sup>Median

6.7 Five protocol amendments occurred prior to the data cut-off date of 7 March 2014. These included changes to patient eligibility criteria and screening requirements, changes to safety and dosage modification requirements, the use of progression free survival as a primary outcome instead of the overall response rate, and an increased sample size. In the publication of MCL-002, the authors stated “Initially, this study was designed to determine the proportion of patients who achieved a response in a controlled but non-comparative fashion, which was later modified to compare progression free survival in a randomised manner comparing lenalidomide with an active monotherapy treatment.” These protocol amendments could potentially have compromised the rigour of the trial. Of the protocol changes, the PBAC agreed with the ESC that the most concerning was the change in primary endpoint. The analysis was not properly adjusted for this, especially the power of the trial. Thus the significance cut-off used might not have been appropriate.

6.8 Patients in the comparator arm of trial MCL-002 received treatment with the participating investigator’s choice of the following agents as monotherapy: fludarabine, gemcitabine, cytarabine, chlorambucil or rituximab. The mixture of

chemotherapy regimens used in the clinical trial might not have been representative of the therapies used in Australian practice. Fludarabine, gemcitabine or cytarabine monotherapy might not be widely used in clinical practice for relapsed or refractory mantle cell lymphoma. On the other hand, ibrutinib is TGA approved for the treatment of patients with mantle cell lymphoma and might be accessed through a compassionate access scheme. However, as ibrutinib is not PBS listed for this indication, the cost-effectiveness has not been established. Similarly, bortezomib combination therapy might be a treatment option, however it is not TGA approved or PBS-listed for relapsed/refractory mantle cell lymphoma (it is TGA registered for use in combination with rituximab, cyclophosphamide, doxorubicin and prednisone in patients with previously untreated mantle cell lymphoma).

### Comparative effectiveness

6.9 Table 3 and Figure 1 summarise the impact of lenalidomide on progression free survival compared with the investigator's choice drugs. The PSCR (p5) provided an update of survival outcomes. The ESC noted that the results were consistent with the data presented in the submission.

The results needed to be interpreted with caution because:

- Patients in the lenalidomide arm were treated until disease progression while cytarabine, fludarabine and gemcitabine were capped at six cycles of treatment;
- The trial was open-label and patients in the investigator's choice arm could receive lenalidomide upon disease progression; and
- There was a high degree of censoring.

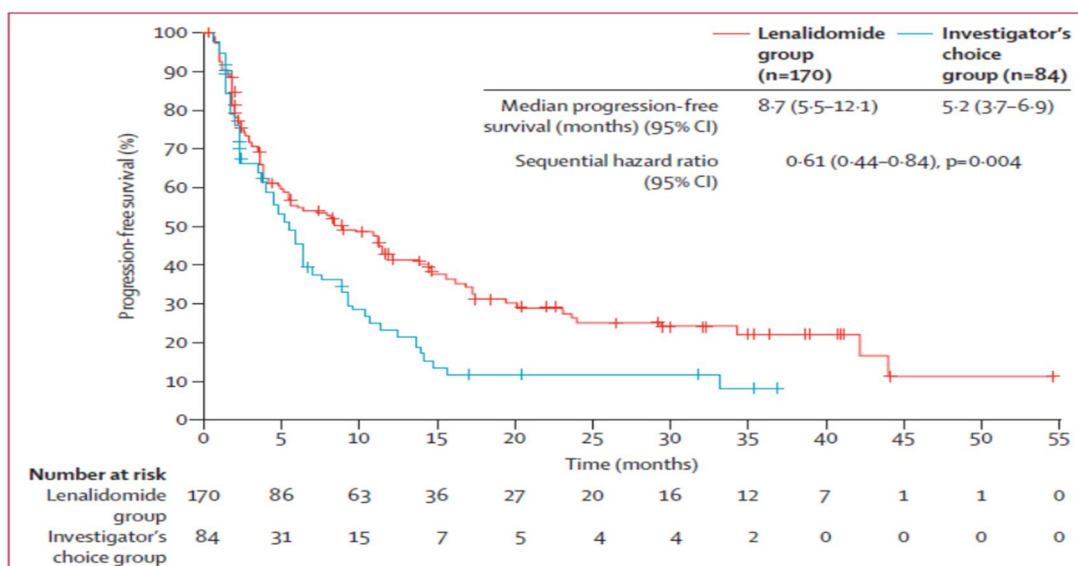
**Table 3: Results of progression free survival for the MCL-002 trial**

|  | <b>Lenalidomide<br/>(N = 170)</b> | <b>Investigator's choice<br/>(N = 84)</b> |
|--|-----------------------------------|---|
| <b>ITT analysis</b> (Median duration of follow-up = 15.9 months) |                                   |   |
| Patients with events n/N (%)                                     | ( ) (%)                           | ( ) (%)                                   |
| Censored n/N (%)   | ( ) (%)                           | ( ) (%)                                   |
| Median PFS, months (95% CI)                                      | 8.7 (5.5, 12.1)                   | 5.2 (3.7, 6.9)                            |
| Sequential HR (95% CI)   | <b>0.61 (0.44, 0.84)</b>          |   |
| Sequential log-rank test, p-value                                | 0.004                             |   |
| Stratified HR (95% CI)   |                                   |   |
| Stratified log-rank test, p-value                                |                                   |   |
| Unstratified log-rank test, p-value                              |                                   |   |

Source: Table B.15, p40 of submission.

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; PFS = progression free survival; **bold** = statistically significant

Figure 1: Progression free survival with lenalidomide compared with investigator's choice in relapsed or refractory mantle cell lymphoma (central review)



Source: Figure 2, p325 Trneny (2016).  
 CI = confidence interval

- 6.10 For the primary analysis, the median duration of follow-up was 15.9 months, with median progression free survival of 8.7 months (95% confidence interval (CI): 5.5 to 12.1) for patients in the lenalidomide group, and 5.2 months (95% CI: 3.7 to 6.9) in the investigator's choice group. Using sequential log-rank testing, a significant reduction in the risk of disease progression or death was observed for patients in the lenalidomide group compared with the comparator group (hazard ratio (HR): 0.61; 95% CI: 0.44 to 0.84). This was also reflected in the stratified analysis (HR: ██████; 95% CI: ██████ to ██████).
- 6.11 Based on the PFS results, the PBAC noted that approximately 40% of patients in both treatment groups progressed within 3-4 months of commencing treatment. However, the response rate with lenalidomide (40%) appeared to be greater than with chemotherapy (11%). The PBAC noted that the progression curves separate at 6 months, which corresponded with the time that the comparator cohort stopped receiving treatment. Thus the difference in progression free survival may be due to the use of lenalidomide beyond 6 months as maintenance treatment. In clinical practice it is likely that the comparator treatments will also be used beyond 6 months and thus the incremental gain in progression free survival may be smaller than demonstrated in the trial.
- 6.12 Table 4 and Figure 2 summarised the impact of lenalidomide on overall survival compared with the investigator's choice arm.

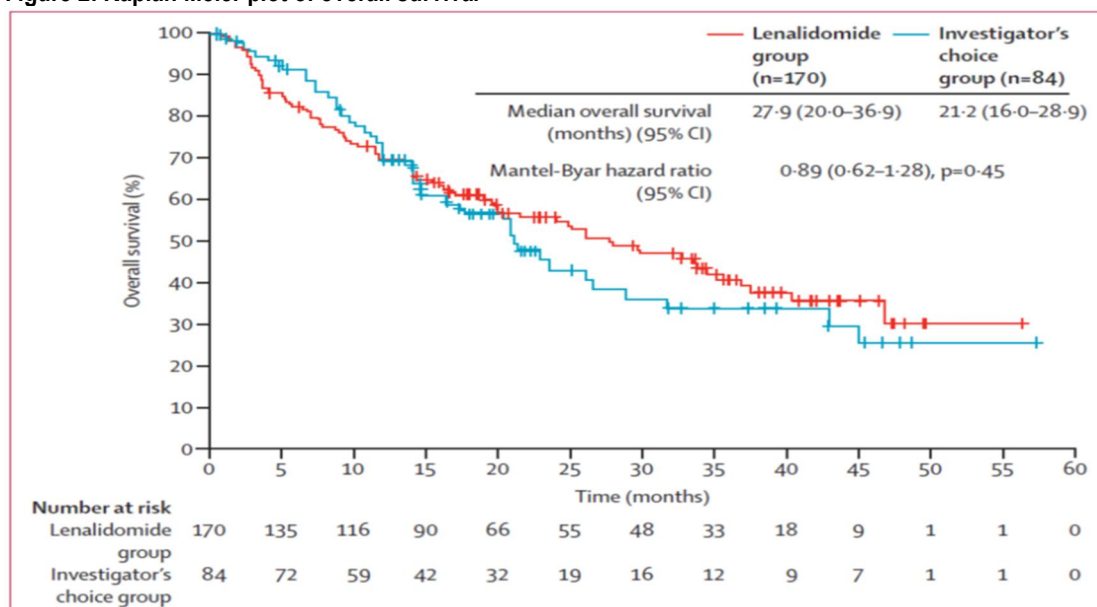
**Table 4: Results of overall survival for the MCL-002 trial**

|  | <b>Lenalidomide<br/>(N = 170)</b> | <b>Investigator's choice<br/>(N = 84)</b> |
|--|-----------------------------------|---|
| <b>ITT analysis</b> (Median duration of follow-up = 15.9 months) |                                   |   |
| Patients with events n/N (%)                                     | ██ (██%)                          | ██ (██%)                                  |
| Median OS, months (95% CI)                                       | 27.9 (20.0, 36.9)                 | 21.2 (16.0, 28.9)                         |
| HR (95% CI)  | 0.89 (0.62, 1.28)                 |   |
| Log-rank test, p-value   | ██                                |   |
| Mantel-Byar test, p-value  | 0.448                             |   |

Source: Table B.15, p40 of submission.

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; OS = overall survival; **bold** = statistically significant

**Figure 2: Kaplan-Meier plot of overall survival**



Source: Figure 4, p327 of Trneny (2016)

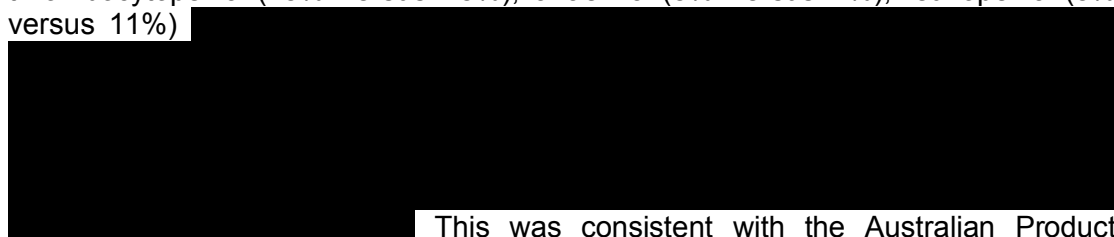
CI = confidence interval

6.13 There was no statistically significant difference in overall survival between lenalidomide and investigator's choice (HR 0.89; 95% CI: 0.62 to 1.28). The submission stated that overall survival was greater for patients treated with lenalidomide. This was inappropriate, as:

- The overall survival gain observed was not significant based on the log-rank and Mantel-Byar tests;
- Patients treated with lenalidomide had lower overall survival in the initial 12 months from randomisation. The submission argued that this was due to patients in the lenalidomide arm having more severe disease, which highlighted issues with randomisation in the MCL-002 trial. The ESC noted that this is the time period in which patients in the comparator arm were receiving treatment; and
- The trial was not designed or powered to demonstrate a significant difference in overall survival.

### **Comparative harms**

- 6.14 Most patients treated with lenalidomide reported at least one treatment emergent adverse event that was Grade 3 or higher (█████% for lenalidomide versus █████% for investigator's choice). The most common treatment emergent Grade 3 or 4 adverse events experienced by patients in the lenalidomide arm were neutropenia (44% versus 34%, lenalidomide versus investigator's choice respectively), thrombocytopenia (18% versus 28%), anaemia (8% versus 7%), leukopenia (8% versus 11%)



This was consistent with the Australian Product Information, which states that patients at a high risk of thromboembolic events should also receive prophylactic treatment with aspirin, warfarin or low-molecular weight heparin.

- 6.15 The ESC noted that following a protocol amendment on 22 March 2013, after all patients were recruited, prophylaxis for thromboembolic events was made mandatory for all patients treated with lenalidomide. This was based upon a recommendation from the data monitoring committee after an observed increase in events in patients treated with lenalidomide. The Australian Product Information indicates prophylactic treatment for thromboembolic events only in those patients at high risk. The economic model and financial estimates did not include the costs associated with prophylactic treatment.
- 6.16 Lenalidomide has a known safety profile with the following identified important risks presented in the Periodic Safety Update Report: teratogenicity; thrombocytopenia and bleeding; neutropenia and infection; thromboembolic events; cutaneous reactions; hypersensitivity; angioedema; and diarrhoea.

### **Benefits/harms**

- 6.17 A summary of the comparative benefits and harms for lenalidomide versus investigator's choice is presented in the table below.

Table 5: Summary of comparative benefits and harms for lenalidomide and investigator's choice in the MCL-002 trial – median duration of follow-up 15.9 months

| Benefits   |                       |                                  |                                 |                                      |                          |                       |
|--|-----------------------|----------------------------------|---------------------------------|--------------------------------------|--------------------------|-----------------------|
|  | Lenalidomide<br>N=170 | Investigator's choice<br>N=84    | Absolute difference<br>(95% CI) | HR (95% CI)                          |                          |                       |
| <b>Progression free survival</b>   |                       |                                  |                                 |                                      |                          |                       |
| Progressed disease; n (%)  | █ (█%)                | █ (█%)                           | █% (█%, █%)                     | -                                    |                          |                       |
| Median; months (95% CI)  | 8.7 (5.5, 12.1)       | 5.2 (3.7, 6.9)                   | -                               | <b>0.61 (0.44, 0.84)</b>             |                          |                       |
| <b>Overall survival</b>  |                       |                                  |                                 |                                      |                          |                       |
| Died; n (%)  | █ (█%)                | █ (█%)                           | █% (█%, █%)                     | -                                    |                          |                       |
| Median; months (95% CI)  | 27.9 (20.0, 36.9)     | 21.2 (16.0, 28.9)                | -                               | 0.89 (0.62, 1.28)                    |                          |                       |
| <b>Harms<sup>a</sup> - Grade 3/4 treatment emergent adverse events<sup>a</sup></b> |                       |                                  |                                 |                                      |                          |                       |
|  | Lenalidomide<br>N=167 | Investigator's<br>choice<br>N=83 | RR<br>(95% CI)                  | Event rate/100 patients <sup>b</sup> |                          | RD<br>(95% CI)        |
|  |                       |                                  |                                 | Lenalidomide                         | Investigator's<br>choice |                       |
| Neutropenia  | 73/167                | 28/83                            | 1.30<br>(0.92, 1.83)            | 44                                   | 34                       | 10.0%<br>(-2.7, 22.6) |
| Thrombocytopenia   | 30/167                | 23/83                            | 0.65<br>(0.40, 1.04)            | 18                                   | 28                       | -9.7%<br>(-2.1, 1.5)  |
| Nervous system disorders   | █/167                 | █/83                             | █<br>(█, █)                     | █                                    | █                        | █%<br>(█, █)          |
| Pulmonary embolism   | █/167                 | █/83                             | █                               | █                                    | █                        | █%<br>(█, █)          |

Source: Table B.15, p40; Table B.16, p42; Table B.24, p49 of the submission and compiled during the evaluation  
 CI = confidence interval; HR = hazard ratio; NC = not calculable; RD = risk difference; RR = relative risk; **bold** = statistically significant

<sup>a</sup> Calculated from safety population

<sup>b</sup> Median duration of follow-up 15.9 months

- 6.18 On the basis of direct evidence presented by the submission, in comparison with investigator's choice of chemotherapy, lenalidomide monotherapy resulted in:
- A reduction of approximately 39% in the risk of disease progression or death over a duration of follow-up of 15.9 months; and
  - No statistically significant improvement in overall survival over a duration of follow-up of 15.9 months.
- 6.19 For every 100 patients treated with lenalidomide in comparison with investigator's choice over a median duration of follow-up of approximately 15.9 months:
- █ more patients will experience Grade 3 or 4 nervous system disorders; and
  - █ more patients will experience Grade 3 or 4 pulmonary embolism.

**Clinical claim**

- 6.20 The submission claimed that lenalidomide was superior in efficacy and non-inferior in safety compared with investigator's choice drugs used in the treatment of patients with relapsed and/or refractory mantle cell lymphoma.
- 6.21 The claim of superior efficacy was not adequately supported given that:
- The trial did not demonstrate significant overall survival gain, which might be partly due to the trial design and the protocol amendments in which the primary outcome was changed from overall response rate to progression free survival. As a result patients were not well matched between treatment arms.
  - The magnitude of benefit might be overstated, as the investigator's choice of

treatment in the trial might not reflect current treatment practices in Australia.

- There was no improvement in progression free survival until four to six months, which could be due to the discontinuation of the comparator treatments, the open-label nature of the trial, the opportunity for patients to cross-over to lenalidomide treatment and the high degree of censoring.
- The clinical trial might not be applicable to the Australian setting:
  - The TGA-approved indication for lenalidomide is not restricted to relapsed or refractory patients with mantle cell lymphoma who are unable to tolerate intensive chemotherapy or stem-cell transplantation; and  
The proposed PBS listing and TGA indication do not restrict lenalidomide to monotherapy treatment. The submission did not provide comparative evidence for lenalidomide in combination therapy, however Phase II studies suggested lenalidomide has potentially greater efficacy, as measured by overall response rate and progression free survival, when used in combination therapy rather than monotherapy.

6.22 The updated survival outcomes provided in the PSCR (p5) were noted, but the PBAC agreed with the ESC that the updated data did not resolve the uncertainty around the clinical claim.

6.23 The claim of non-inferior safety of lenalidomide was not reasonable as:

- Lenalidomide was associated with higher rates of Grade 3 or 4 adverse events when compared with the control arm; and
- The duration of treatment observed in the MCL-002 trial might not reflect clinical practice. When compared with the MCL-002 trial, the treatment periods might be longer for lenalidomide in clinical practice.

### **Economic analysis**

6.24 The submission presented a modelled cost-effectiveness analysis. A Markov-like partitioned survival model was used with the following three health states:

- pre-progression;
- post-progression; and
- death from any cause.

6.25 All patients began in the pre-progression health state and were treated with either lenalidomide or a weighted mix of investigator's choice drug. During any given cycle, patients could be alive in the pre-progression or post-progression health states, or dead. Patients free of progression were assumed to continue with lenalidomide, or continue with the investigator's choice drug until the maximum duration of treatment was achieved. Upon disease progression, patients discontinued their respective treatment and could move to second-line treatment. Transitions between health states were one-directional due to the aggressive nature of relapsed and/or refractory mantle cell lymphoma. Table 6 summarises the model structure and rationale.

**Table 6: Summary of model structure and rationale**

| Component                        | Summary   |
|----------------------------------|---|
| Time horizon                     | 10 years in the model base case versus a median follow-up of 15.9 months in the trial<br>Updated to 8 years in the base case presented in the pre-PBAC response |
| Outcomes                         | LYG and QALYs   |
| Methods used to generate results | Markov model; cohort expected value analysis with univariate and deterministic sensitivity analyses   |
| Cycle length                     | 7 days  |
| Transition probabilities         | Weibull, based on Kaplan-Meier curves for PFS and OS and extrapolation of the curves  |
| Utilities                        | Transformed EORTC QLC C-30 baseline to EQ 5D values (pre-progressed state = 0.71)<br>progressed state = 0.71-0.24 = 0.47) <sup>a</sup>                          |

Source: compiled during the evaluation

LYG = life years gained; OS = overall survival; PFS = progression free survival; QALY= quality-adjusted life year

<sup>a</sup> Note that the 0.24 refers to the difference between pre-progression and post-progression for patients with aggressive NHL in a study by Dooduijn et al (2005)

6.26 The PBAC noted a number of changes to the model base case were presented in the pre-PBAC response:

- the time horizon of the model was changed from 10 years to 8 years;
- the model used the weighted average cost of lenalidomide across all strengths as informed by the current average daily dose of lenalidomide in patients currently accessing the drug through the Sponsor's access program;
- reduction of ■■■% on the effective price.

The changes to the time horizon and calculation of the weighted price of lenalidomide were both consistent with recommendations from the ESC advice, and both changes increased the ICER. The price reduction reduced the ICER.

6.27 A summary of the key drivers of the model is presented in Table 7 below.

**Table 7: Key drivers of the model**

| Description                    | Method/Value  | Impact   |
|--------------------------------|---|--|
| Outcomes extrapolation method  | Use of Weibull parametric modelling to extrapolate PFS and OS   | High, favours lenalidomide   |
| Overall survival advantage     | Assumption of significant OS advantage for patients treated with lenalidomide   | High, favours lenalidomide   |
| Rituximab maintenance therapy  | Rituximab maintenance therapy was assumed to continue for more than four cycles   | Moderate, favours lenalidomide   |
| Weighted price of lenalidomide | Assumption that all patients would receive 0.7 scripts of the 25 mg lenalidomide strength every four weeks.<br>Changed to a weighted average daily cost of lenalidomide based on current usage experience in the Sponsor's Pre-PBAC response. | High, however the re-specified base case from the Pre-PBAC response was considered to adequately address this. |

Source: compiled during the evaluation

OS = overall survival; PFS = progression free survival

6.28 The submission modelled continued OS benefit when there was no statistically significant overall survival benefit observed in the MCL-002 trial. The model's assumption that lenalidomide was associated with an overall survival advantage compared with investigator's choice drugs was a key driver of the economic model.

The PBAC considered that modelling a benefit in OS was inappropriate when no statistically significant difference was observed in the trial.

- 6.29 The ESC considered that the utilities used in the model were not well supported, and noted that there was no significant difference in the quality of life observed between the lenalidomide treated cohort and the comparator cohort in the study. However, sensitivity analyses (see below) showed that this was not a strong driver of the model.
- 6.30 The results of the cost-effectiveness analysis are presented in Table 8 below.

**Table 8: Results of the economic evaluation**

| Component   | Lenalidomide  | Investigator's choice | Increment            |
|---|---------------|-----------------------|----------------------|
| Costs (discounted)*   | \$ [REDACTED] | \$ [REDACTED]         | \$ [REDACTED]        |
| LYG   | 2.89          | 2.28                  | 0.61                 |
| QALYs   | 1.59          | 1.21                  | 0.37                 |
| Incremental cost/extra LYG  |               |                       | \$ [REDACTED]        |
| Incremental cost/extra QALY gained – submission                         |               |                       | \$ [REDACTED]        |
| Incremental cost/extra QALY gained – updated analysis presented in PSCR |               |                       | \$ [REDACTED]        |
| <b>Respecified base case presented in pre-PBAC response</b>             |               |                       |                      |
| Costs   |               |                       | \$ [REDACTED]        |
| LYG   |               |                       | 0.51                 |
| QALYs   |               |                       | 0.37                 |
| Cost/LY   |               |                       | \$ [REDACTED]        |
| <b>Cost/QALY</b>  |               |                       | <b>\$ [REDACTED]</b> |

Source: Section D Workbook.xlsx worksheet 'Results'

LYG = life-years gained; QALY= quality-adjusted life year

- 6.31 The incremental cost-effectiveness ratio (ICER) presented in the submission was updated in the PSCR to reflect 1 April 2016 price changes. The pre-PBAC response presented a re-specified base case, with an estimated ICER of \$45,000/QALY - \$75,000/QALY.

The PBAC noted that the re-specified base case addressed some of the issues raised in the Commentary and ESC advice, but the Committee were of the view that the ICER remained highly optimistic due to:

- The assumption that patients treated with lenalidomide had continued overall survival gains over patients treated with chemotherapy regimens. This was not supported by the clinical data from the MCL-002 trial, which showed no statistically significant advantage in overall survival between the lenalidomide and investigator's choice groups. The continued OS benefit at five years and beyond in the model was implausible.
- The use of Weibull parametric modelling in the extrapolation of overall survival beyond the trial period, despite the lack of goodness-of-fit.
  - This method did not have good internal validity, when tested during evaluation and external validity was not tested in the submission; and
  - The entire duration of the Kaplan-Meier curve was used (up to five years), while the median duration of follow-up in the trial was 15.9 months. An updated Section D workbook was provided with the PSCR, directly applying trial data up to 69 weeks (consistent with the median follow-up of 68.7

weeks [15.9 months] for all patients) prior to extrapolation. This resulted in an ICER of \$45,000/QALY - \$75,000/QALY.

- The assumption that rituximab would be used for more than four cycles in maintenance therapy for relapsed/refractory mantle cell lymphoma. This is longer than is currently permitted under the PBS restriction and overestimated the cost of the comparator.
- The 10 year time horizon of the model was inappropriate given the nature of the disease. The ESC considered that an 8 year time horizon would be more appropriate. The PBAC noted that the re-specified base case in the pre-PBAC response was 8 years, but considered that this time horizon remained optimistic in this cohort of patients.
- The Australian Product Information indicates prophylactic treatment for thromboembolic events in patients at high risk. The economic model did not include the costs associated with prophylactic treatment.
- The PBAC noted that the cost of the i-access program, that is required for patients being treated with lenalidomide, was not included in the economic analysis.

6.32 Table 9 presents the sensitivity analyses conducted during the evaluation. Additional sensitivity analyses around the re-specified base case from the Pre-PBAC response were not provided.

**Table 9: Results of key univariate sensitivity analyses using updated prices (1 April 2016)**

| Univariate analyses   | Δ costs       | Δ QALY | Incremental cost-effectiveness |
|---|---------------|--------|--------------------------------|
| <b>Base case</b>  | \$ [redacted] | 0.37   | \$ [redacted]                  |
| <b>Time horizon (base case 10 year)</b>   |               |        |                                |
| 5 year  | \$ [redacted] | 0.22   | \$ [redacted]                  |
| 8 year  | \$ [redacted] | 0.33   | \$ [redacted]                  |
| <b>Extrapolation of overall survival (base case: Weibull modelling)</b>   |               |        |                                |
| Exponential modelling   | \$ [redacted] | 0.28   | \$ [redacted]                  |
| No overall survival advantage <sup>a</sup>  | \$ [redacted] | 0.08   | \$ [redacted]                  |
| <b>Utilities (base case: 0.71; 0.47)</b>  |               |        |                                |
| Hornberger and Best (0.83, 0.38)  | \$ [redacted] | 0.40   | \$ [redacted]                  |
| Doorduijn (0.74, 0.50)  | \$ [redacted] | 0.39   | \$ [redacted]                  |
| <b>Additional sensitivity analyses conducted during evaluation</b>  |               |        |                                |
| Lenalidomide weighted price (base case: 25 mg)<br>Split based on relapsed MM prescribing <sup>b</sup>                         | \$ [redacted] | 0.37   | \$ [redacted]                  |
| No rituximab maintenance therapy for comparator arm (base case rituximab until disease progression)                           | \$ [redacted] | 0.37   | \$ [redacted]                  |
| <b>Additional sensitivity analysis presented in PSCR</b>  |               |        |                                |
| Correction of chemotherapy administration costs plus direct application of trial survival data to 69 weeks then extrapolation | \$ [redacted] | 0.4    | \$ [redacted]                  |

Source: Section D Workbook.xlsx and compiled during the submission.

MM = multiple myeloma; QALY = quality-adjusted life year

<sup>a</sup> This was modelled by assuming that lenalidomide would have the same overall survival probability as investigator's choice.

<sup>b</sup> Assuming [redacted]% for 5 mg, [redacted]% for 10 mg, [redacted]% for 15 mg and [redacted]% for 25 mg strength, based on lenalidomide prescribing for progressive multiple myeloma between 1 July 2014 and 30 June 2015.

The redacted table shows the base case ICER is in the range of \$45,000/QALY - \$75,000/QALY, \$75,000 - \$105,000/QALY and more than \$200,000/QALY.

**Drug cost/patient/course: \$ [REDACTED] (based on price offered in the submission)**

6.33 The drug cost of \$ [REDACTED] per patient for lenalidomide was compared with a treatment cost of \$836 for a full course of chlorambucil, \$9,481 for cytarabine, \$10,545 for fludarabine; \$1,825 for gemcitabine and \$50,927 for four cycles of rituximab.

**Estimated PBS usage & financial implications**

6.34 This submission was not considered by DUSC.

6.35 An epidemiological approach was used to estimate the incidence of relapsed and/or refractory mantle cell lymphoma. Updated estimates were presented with the pre-PBAC response, which incorporated the updated proposed pricing for lenalidomide with utilisation based on a weighted cost across strengths. Table 10 summarises the estimated use and financial implications associated with lenalidomide monotherapy for relapsed and/or refractory mantle cell lymphoma.

**Table 10: Estimated use and financial implications**

|  | Year 1         | Year 2         | Year 3         | Year 4         | Year 5         |
|--|----------------|----------------|----------------|----------------|----------------|
| <b>Estimated extent of use</b>   |                |                |                |                |                |
| Number treated   | [REDACTED]     | [REDACTED]     | [REDACTED]     | [REDACTED]     | [REDACTED]     |
| Scripts <sup>a</sup>   | [REDACTED]     | [REDACTED]     | [REDACTED]     | [REDACTED]     | [REDACTED]     |
| <b>Estimated net cost to PBS/RPBS/MBS (as estimated in the submission)</b>                             |                |                |                |                |                |
| Net cost to PBS/RPBS   | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  |
| Net cost to MBS  | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] |
| Net cost to hospital budgets   | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] |
| <b>Estimated total net cost</b>  |                |                |                |                |                |
| <b>Total net cost to Government</b>  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  |
| <b>Estimated net changes to Government health budgets (re-analysis presented in pre-PBAC response)</b> |                |                |                |                |                |
| Net cost to PBS/RPBS   | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  |
| Net impact on other budgets  | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] |
| <b>Total net cost to Government</b>  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  | \$ [REDACTED]  |

Source: Table E.9, p106 of the submission updated to 1 April 2016 prices and calculated during the evaluation.

Tab E5 of Section E workbook provided in the Pre-PBAC Response based on re-specified base case.

MBS = Medicare Benefits Schedule; (R)PBS = (Repatriation) Pharmaceutical Benefits Scheme

<sup>a</sup> Assuming 8.11 scripts per patient per year as estimated during the evaluation

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million per year.

6.36 The submission estimated a total net cost of \$10 – \$20 million to the PBS/RPBS/MBS over the first five years of listing (based on 1 April 2016 prices). The re-analysis presented in the pre-PBAC response estimated a cost of approximately \$10 – \$20 million to the PBS/RPBS/MBS. There was potential for the cost to the government to be lower or higher than the presented estimate as:

- The net cost to the PBS/RPBS might be higher or lower due to:
  - The unclear estimation of the incidence of relapsed and/or refractory mantle cell lymphoma and uptake of lenalidomide (overestimate);
  - The assumption that patients would receive [REDACTED] scripts of the 25 mg strength per 4-week cycle, rather than a weighted average of full scripts of the various

- available strengths (underestimate);
- The assumption that lenalidomide monotherapy would completely replace the drugs used in the investigator's choice arm (underestimate);
- Differences between the drugs selected in the investigator's choice arm for the MCL-002 trial and unknown current practice in Australian (unclear); and
- Costs associated with co-administered therapies for thromboembolic prophylaxis and treatment-emergent adverse events were not included (underestimate).
- The net cost to the MBS might be higher due to:
  - Uncertainty around the true number of investigator's choice drugs that will be substituted by lenalidomide (underestimate); and
  - The exclusion of health care resources as described in the Australian Product Information, such as those incurred in running the i-access<sup>®</sup> program (underestimate).

### **Quality Use of Medicines**

- 6.37 The submission noted that lenalidomide is a thalidomide derivative, and patients must be enrolled in the i-access<sup>®</sup> program. Details of the i-access<sup>®</sup> program are presented in the Australian Product Information.

### **Financial Management – Risk Sharing Arrangements**

- 6.38 The ESC noted that the Sponsor stated they were willing to consider a Risk Share Agreement in the PSCR.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **7 PBAC Outcome**

- 7.1 The PBAC rejected the listing of lenalidomide on the basis of uncertain effectiveness, with no overall survival gain demonstrated in the trial, and uncertain cost-effectiveness. The PBAC noted that the re-specified base case presented in the pre-PBAC response addressed some of the issues raised with the economic evaluation, but were of the view that many assumptions used in the estimation of the cost-effectiveness remained optimistic, and that the ICER was therefore likely to be higher than estimated in the submission.
- 7.2 The PBAC recognised that there is a need for a treatment option that induces a high response rate with minimal toxicity for patients with relapsed/refractory mantle cell lymphoma, who are unsuitable for chemotherapy. The Committee considered that the appropriate clinical place for lenalidomide if listed would be in the management of patients for whom there are currently no PBS subsidised treatments. The extent to which the addition of lenalidomide would improve management in this population of patients with poor prognosis remains unknown.
- 7.3 The PBAC considered the comparator was appropriate, however acknowledged advice received from the Australian Leukaemia and Lymphoma Group that highlighted the highly fluid nature of the treatment algorithm for this cohort of

patients.

- 7.4 In regard to the clinical evidence presented in the submission, the PBAC noted that there were five protocol amendments to the clinical trial (MCL-002) prior to the data cut-off date, which could potentially have compromised the rigour of the trial. Of the protocol changes, the PBAC agreed with the ESC that the most concerning was the change in primary endpoint. The analysis was not properly adjusted for this, especially the power of the trial. Thus, the significance cut-off used might not have been appropriate.
- 7.5 The chemotherapy regimens in the comparator arm of MCL-002 were the participating investigator's choice of the following agents as monotherapy: fludarabine, gemcitabine, cytarabine, chlorambucil or rituximab. Whether the chemotherapy regimens used in the clinical trial were representative of the therapies used in Australian practice was not well supported in the submission. Furthermore, the PBAC noted that treatment of the comparator cohort ceased at 6 months in the study, whereas in clinical practice treatment is likely to continue beyond this point.
- 7.6 Based on the PFS results, the PBAC noted that approximately 40% of patients in both treatment groups progressed within 3-4 months of commencing treatment. However, the response rate with lenalidomide (40%) appeared to be greater than with chemotherapy (11%). The PBAC noted that the progression curves separate at 6 months, which corresponded with the time that the comparator cohort stopped receiving treatment. Thus, the difference in progression free survival may be due to the use of lenalidomide beyond 6 months as maintenance treatment. In clinical practice it is likely that the comparator treatments will also be used beyond 6 months and thus the incremental gain in progression free survival may be smaller than demonstrated in the trial.
- 7.7 Based on the issues with the clinical trial, the Committee considered it was difficult to make a reliable estimate of any benefit that lenalidomide would add to the management of relapsed/refractory mantle cell lymphoma patients.
- 7.8 The PBAC did not accept the submission's claim of non-inferior comparative safety, noting that lenalidomide was associated with higher rates of Grade 3 or 4 adverse events when compared with the control arm.
- 7.9 The PBAC noted the adjusted time horizon for the economic evaluation from 10 years to 8 years in the Pre-PBAC response. While this was considered more appropriate for relapsed/refractory mantle cell lymphoma, the Committee was of the view that it was still an unrealistically long time horizon for this cohort of patients. The PBAC noted that the continued OS benefit presented at 5 years and beyond in the model is implausible, and considered that modelling a benefit in OS was inappropriate when no statistically significant difference was observed in the trial.
- 7.10 Overall, the PBAC considered that the ICER presented was based on optimistic assumptions, and therefore unlikely to give a reasonable estimate of the cost-effectiveness of lenalidomide in the relapsed/refractory mantle cell lymphoma population. The following issues with the model remained of particular concern:
- The assumption that patients treated with lenalidomide had continued overall survival gains over patients treated with chemotherapy regimens. This was not

supported by the clinical data from the MCL-002 trial, which showed no statistically significant advantage in overall survival between the lenalidomide and investigator's choice groups.

- The use of Weibull parametric modelling in the extrapolation of overall survival beyond the trial period, despite the lack of goodness-of-fit.
- The assumption that rituximab would be used for more than four cycles in maintenance therapy for relapsed/refractory mantle cell lymphoma. This is longer than is currently permitted under the PBS restriction and overestimated the cost of the comparator.
- The time horizon of the model was inappropriate given the nature of the disease. The PBAC noted that the re-specified base case in the pre-PBAC response was 8 years, but considered that this time horizon remained optimistic in this cohort of patients.
- The Australian Product Information indicates prophylactic treatment for thromboembolic events in patients at high risk. The economic model did not include the costs associated with prophylactic treatment.
- The PBAC noted that the cost of the i-access program, that is required for patients being treated with lenalidomide, was not included in the economic analysis.

7.11 The PBAC recommended that any resubmission should address the issues with the economic model noted in 7.10 and therefore would need to be a major submission to allow for re-evaluation of the economic model.

7.12 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 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.

## **9 Sponsor's Comment**

The inability for Celgene to advance negotiations with the PBAC is reflective of the challenges facing companies trying to make novel therapies for orphan indications available to Australian patients.