

## 6.03 LENALIDOMIDE, CAPSULE, 5 MG, 10 MG AND 15 MG, REVLIMID<sup>®</sup>, CELGENE PTY LTD.

### 1 Purpose of Application

- 1.1 Section 100 (HSD) listing for lenalidomide for use as maintenance therapy in patients with newly diagnosed multiple myeloma (NDMM) who have undergone an autologous stem cell transplant (ASCT). An application specifically for use as maintenance therapy following first line ASCT in MM has not been previously considered by the PBAC.

**Table 1: Key components of the clinical issue addressed by the submission**

| Component      | Description   |
|----------------|---|
| Population     | NDMM patients who have undergone ASCT.  |
| Intervention   | Maintenance therapy with lenalidomide.  |
| Comparator     | Main comparator: best supportive care (BSC) defined as 'no maintenance therapy' or observation.<br>Secondary comparator: maintenance therapy with thalidomide.  |
| Outcomes       | PFS, OS, PFS after next line therapy (PFS2) and response rate.  |
| Clinical claim | In NDMM post-ASCT, <ul style="list-style-type: none"> <li>lenalidomide has superior comparative efficacy (OS and PFS) and inferior comparative safety than BSC.</li> <li>lenalidomide has superior comparative OS, non-inferior PFS and different safety than thalidomide.</li> </ul> |

Abbreviations: ASCT = autologous stem cell transplant; BSC = best supportive care; NDMM = newly diagnosed multiple myeloma; OS = overall survival; PFS = progression free survival; PFS2 = progression free survival after next line of therapy.

Source: Table 1.1.1, p.20 of the submission.

### 2 Requested listing

- 2.1 The sponsor requested listing is shown below. Suggestions and additions to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

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| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Dispensed Price for Max. Qty            | Proprietary Name and Manufacturer |
|--|----------|-------------|---|-----------------------------------|
| Lenalidomide, Capsule, 5 mg, 28                      | 1        | 5-2         | \$ [REDACTED] published price (public)  | Revlimid® Celgene Pty Ltd         |
|  |          |             | \$ [REDACTED] published price (private) |                                   |
|  |          |             | \$ [REDACTED] effective price (public)  |                                   |
|  |          |             | \$ [REDACTED] effective price (private) |                                   |
| Lenalidomide, Capsule, 10 mg, 28                     | 1        | 5-2         | \$ [REDACTED] published price (public)  | Revlimid® Celgene Pty Ltd         |
|  |          |             | \$ [REDACTED] published price (private) |                                   |
|  |          |             | \$ [REDACTED] effective price (public)  |                                   |
|  |          |             | \$ [REDACTED] effective price (private) |                                   |
| Lenalidomide, Capsule, 15 mg, 28                     | 1        | 5-2         | \$ [REDACTED] published price (public)  | Revlimid® Celgene Pty Ltd         |
|  |          |             | \$ [REDACTED] published price (private) |                                   |
|  |          |             | \$ [REDACTED] effective price (public)  |                                   |
|  |          |             | \$ [REDACTED] effective price (private) |                                   |

|                      |  |
|----------------------|--|
| Category/Program:    | Section 100 – HSD  |
| PBS indication:      | Multiple Myeloma   |
| Treatment phase:     | Initial  |
| Restriction:         | Authority Required – In Writing  |
| Clinical criteria:   | <ul style="list-style-type: none"> <li>• <del>The condition must be newly diagnosed;</del></li> <li>AND</li> <li>• <del>The condition must be confirmed by a histological diagnosis;</del></li> <li>AND</li> <li>• The treatment must be as monotherapy; OR</li> <li>• <del>The treatment must be in combination with dexamethasone;</del></li> <li>AND</li> <li>• Patient must have undergone <del>a primary</del> an autologous stem cell transplant as part of frontline therapy for newly diagnosed multiple myeloma</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Patient must not have progressive disease following autologous stem cell transplant</li> </ul>   |
| Prescriber criteria: | <p>The authority application must be made in writing and must include:</p> <p>(1) a completed authority prescription form; and</p> <p>(2) a completed Multiple Myeloma lenalidomide Authority Application - Supporting Information Form, which includes details of the histological diagnosis of multiple myeloma; <del>and ineligibility for prior details of autologous stem cell transplant;</del> and nomination of which disease activity parameters will be used to assess response progression; and</p> <p>(3) a signed patient acknowledgement.</p> <p>To enable confirmation of eligibility for treatment, current diagnostic reports of at least one of the following must be provided:</p> <p>(a) the level of serum monoclonal protein; or</p> <p>(b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or</p> <p>(c) the serum level of free kappa and lambda light chains; or</p> <p>(d) bone marrow aspirate or trephine; or</p> <p>(e) if present, the size and location of lytic bone lesions (not including compression fractures); or</p> <p>(f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or</p> <p>(g) if present, the level of hypercalcaemia, corrected for albumin concentration.</p> <p>As these parameters will be used to determine response progression, results for either (a) or (b) or (c) should be provided for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) should be provided. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or</p> |

|  |  |
|--|--|
|  | non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be provided.<br>Patient must be registered in the i-access risk management program. |
|--|--|

- 2.2 The submission proposed a special pricing arrangement with published and effective prices as presented above.
- 2.3 The proposed restriction is largely consistent with the use of lenalidomide in the CALGB trial (the main source of the evidence comparing lenalidomide with BSC), the proposed TGA PI and the Medical Scientific Advisory Group (MSAG) to the Myeloma Foundation of Australia clinical guidelines for the treatment of multiple myeloma. However, in the approved TGA PI and the clinical evidence presented in the submission, the use of lenalidomide in patients with NDMM post-ASCT is not in combination with dexamethasone (as requested in the restriction). The PBAC agreed with the ESC that use should be restricted to monotherapy for this indication.
- 2.4 The ESC considered that there was the potential for this restriction to be interpreted more broadly than intended, such that lenalidomide maintenance could be used at any time after an ASCT. While accepting that there was some risk of this, the PBAC considered that it was unlikely to be of sufficient magnitude to require the restriction to specify a time period cut off for commencement of maintenance. The PBAC noted that some patients may receive tandem transplants and considered that the restriction should not preclude these patients from receiving maintenance treatment.
- 2.5 The PBAC considered that it may be more appropriate to provide three months treatment per prescription, instead of the requested six, as patients receiving lenalidomide maintenance treatment should be regularly reviewed by a medical practitioner. The PBAC also considered that, consistent with the lenalidomide restriction for the treatment of relapsed or refractory multiple myeloma, it may be reasonable for continuing scripts to be telephone authority.

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

### **3 Background**

#### ***Registration status***

- 3.1 TGA status at time of PBAC consideration: The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, lenalidomide was TGA registered “For the maintenance treatment of patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.”
- 3.2 The recommended dosing regimen for lenalidomide for use in the maintenance setting (NDMM post-ASCT) is 10 mg orally once daily, increasing to 15 mg/day after 3 months of therapy if tolerated, with patients continuing therapy until disease progression or intolerance. The PBAC noted lower doses were used in the clinical trials presented in the submission (e.g. 10 mg/day for 21/28 days) and these may be clinically appropriate and used in clinical practice.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

### **4 Population and disease**

- 4.1 Multiple myeloma (MM) is a malignant plasma cell proliferation. The uncontrolled growth of myeloma cells can lead to skeletal destruction, bone marrow failure, increased plasma volume and viscosity, suppression of normal immunoglobulin production and renal insufficiency. In the symptomatic phase, the most common symptom is bone pain. MM is characterised by periods of remission post-treatment which are followed by relapse.
- 4.2 The PBS listing for lenalidomide proposed in this submission is as post-ASCT maintenance treatment for patients with NDMM.
- 4.3 Lenalidomide is an immunomodulatory drug (IMiD). IMiDs have both immunomodulatory and anti-angiogenic properties which could confer anti-tumour and anti-metastatic effects.

### **5 Comparator**

- 5.1 The submission nominated best supportive care (BSC) as the main comparator which is defined as ‘no maintenance therapy’ or observation. The main justification was that there are no medicines approved by the TGA for maintenance therapy for NDMM post-ASCT.
- 5.2 The submission nominated thalidomide as a secondary comparator as thalidomide is used in Australia, off-label, in the maintenance setting. Thalidomide is also an IMiD. The submission argued that thalidomide “is not considered to be a true ‘maintenance therapy’” (p.24 of the submission) because its toxicity and lack of tolerability as long-term therapy have resulted in treatment being capped at

12 months. However, the PBAC noted that Australian clinical guidelines (MSAG to the Myeloma Foundation of Australia Guidelines 2017) recommend the use of thalidomide (100 mg daily with or without corticosteroids) as maintenance therapy for approximately 12 months.

- 5.3 Data presented in the submission from the Myeloma and Related Diseases Registry (MRDR) and updated in the Pre-Sub-Committee Response (PSCR) indicated that approximately [REDACTED]% of MM patients who undergo an ASCT do not receive any active maintenance therapy. Of the remainder ([REDACTED]%), [REDACTED]% receive maintenance therapy with thalidomide ([REDACTED]% of the total population). The ESC noted that a presentation from the MRDR<sup>1</sup> reported that in a sample of patients between 2012 and 2015 “maintenance therapy was used in 105 (64.4%) of patients post-ASCT with thalidomide containing therapy most frequent (73%) [47.0% of total population]”. The ESC considered that maintenance treatment, and the use of thalidomide for such treatment, was increasing in Australia, and therefore the proportion of both has likely increased in the time since this sample was taken. The pre-PBAC response (p1) acknowledged the updated MRDR data, however maintained it supported BSC as an appropriate comparator. The PBAC considered that although the data from the MRDR was an appropriate source to ascertain the treatments used post-ASCT, there were some limitations with this source, particularly because of the limited information on the completeness of this data set, quality control measures, and how missing data are accounted for.
- 5.4 Although thalidomide is not TGA approved for use as maintenance therapy, the current PBS listing is broad, and there is evidence of considerable use in this setting. Thalidomide is less costly than lenalidomide and is an alternative therapy that is likely to be replaced in practice.
- 5.5 The PBAC noted that thalidomide was recommended and used as maintenance treatment post-ASCT in current Australian clinical practice. The PBAC also noted the data presented by the submission indicated that not all patients receive thalidomide, with a proportion receiving BSC (no active maintenance treatment). The PBAC considered the majority of patients who do not receive thalidomide post-ASCT are those patients unable to tolerate thalidomide due to adverse events such as neuropathy, somnolence and constipation. The PBAC considered, if listed, these patients would be treated with lenalidomide. Thus, the PBAC considered a mixed comparator of thalidomide and BSC to be reasonable, however noted the weightings that should be applied to each treatment was unclear and inadequately justified in the submission.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

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<sup>1</sup> Bergin K, *et al* 2017. Rates of Upfront Autologous Stem Cell Transplantation in Newly Diagnosed Multiple Myeloma: A report from the MRDR. 16<sup>th</sup> International Myeloma Workshop: e30

## 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 individuals (199), health care professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with lenalidomide. In particular, consumers highlighted the benefit of avoiding the peripheral neuropathy that can be experienced with thalidomide. While some consumers noted that they still experienced side effects with lenalidomide, they were also of the view that the lenalidomide side effects were more manageable and some patients had the ability to return to work, which they valued. A number of consumers cited cost as a barrier to accessing lenalidomide treatment in the absence of PBS subsidy.
- 6.3 The PBAC noted the advice from Myeloma Australia and the South East Myeloma Support Group SA that access to lenalidomide may result in fewer side effects than experienced on thalidomide and that the side effects experienced with thalidomide, such as peripheral neuropathy, constipation, and fatigue, have an impact on quality of life.

### ***Clinical trials***

- 6.4 The submission was based on four randomised trials. Two trials compared lenalidomide to placebo following ASCT (CALGB n=460, IFM 2005-02 n=614). Two included ASCT and non-ASCT patients receiving lenalidomide maintenance compared to BSC and thus relied on subgroup analyses (GIMEMA n=135, Myeloma XI n=788).
- 6.5 No head-to-head trials were identified comparing lenalidomide and thalidomide. Therefore, an indirect comparison was conducted. The submission included one randomised trial comparing thalidomide to observation (Myeloma IX n=493), which was used to form an indirect comparison with lenalidomide via BSC as a common reference. An independent search located two potentially relevant trials: the MM6 and Myeloma X trials. MM6 (n=243), was an Australasian Leukaemia & Lymphoma Group (ALLG) trial published by Kalff et al. (2014) and Spencer et al. (2009), which compared thalidomide with prednisolone alone for maintenance post-ASCT in patients with NDMM. Excluding the MM6 trial from the submission biased the indirect comparison between lenalidomide and thalidomide in favour of lenalidomide.
- 6.6 Myeloma X, published by Stewart et al. (2013), reported the use of thalidomide for ongoing maintenance (over 4 years) at a dose up to 200 mg/day. The key results

from Myeloma X are presented as supplementary evidence for thalidomide on the basis that the dose range is higher than recommended in the MSAG Guidelines.

6.7 The PBAC noted the 2012 IMWG consensus paper<sup>2</sup> for maintenance therapy in MM included 7 thalidomide trials.

6.8 Details of the trials presented in the submission are provided in the table below.

**Table 2: Trials and associated reports presented in the submission**

| Trial ID     | Protocol title/ Publication title   | Publication citation  |
|--------------|---|---|
| Lenalidomide |   |   |
| CALGB        | CSR. A Phase III Randomized, Double-Blind Study of Maintenance Therapy with Lenalidomide CC-5013 (NSC#703813, IND #70116) or Placebo Following Autologous Stem Cell Transplantation for Multiple Myeloma  | January 2016  |
| NCT00114101  | Holstein SA, Jung S-H, Richardson PG et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial   | Lancet Haematol 2017; 4(9):e431-442   |
|              | BresMed 'Adjustment for treatment cross-over in the Cancer and Leukaemia Group B (CALGB) trial in multiple myeloma: Statistical analysis report'  | Feb 23 2017   |
|              | McCarthy PL, Owzar K, Hofmeister CC et al. Lenalidomide after stem-cell transplantation for multiple myeloma  | N Engl J Med; 2012; 366(19):1770-81   |
|              | McCarthy PL, Holstein SA, Jung S-H et al. CALGB/ECOG 100104 (Alliance) study: Lenalidomide (LEN) vs placebo (PBO) maintenance (maint) after stem cell transplant (SCT) for patients (pts) with multiple myeloma-Overall survival (OS) and progression-free survival (PFS) adjusted for treatment (tx) cross-over (XO)   | Journal of Clinical Oncology; 35:15 Supplement 1  |
|              | McCarthy PL, Owzar K, Hofmeister CC et al. Analysis of overall survival (OS) in the context of cross-over from placebo to lenalidomide and the incidence of second primary malignancies (SPM) in the phase iii study of lenalidomide versus placebo maintenance therapy following autologous stem cell transplant (ASCT) for multiple myeloma (MM) CALGB (alliance) ECOG BMTCTN 100104' | Clinical Lymphoma, Myeloma and Leukemia 2013; 13:28   |
|              | McCarthy PL, Owzar K, Anderson KC, Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB 100104  | Blood 2010; Conference: 52nd Annual Meeting of the American Society of Hematology, ASH. 21; 116 |
|              | McCarthy PL et al. 'Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): Calgb ecog BMT-CTN 100104'.  | Haematologica 2011; 96:S23  |
| IFM 2005-02  | CSR. Benefit of A Maintenance Treatment With Lenalidomide Following Autologous Stem Cell Transplantation in Patients With Myeloma Aged Less Than 65 Years   | 29 April 2016   |
| NCT00430365  | Attal M, Lauwers-Cances V, Marit G et al., Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma  | N Engl J Med 2012; 2012366(19):1782-91  |
|              | Attal M, Lauwers-Cances V, Marit G et al., Lenalidomide maintenance after stem-cell transplantation for multiple myeloma: Follow-up analysis of the   | Blood 2013; Conference: 55th Annual Meeting of the  |

<sup>2</sup> Blood. 2012;119(13):3003-3015

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| Trial ID                                | Protocol title/ Publication title   | Publication citation   |
|---|---|--|
|   | <p>IFM 2005-02 trial</p> <p>Marit G, Lauwer-Cances V, Caillot D et al., Prognostic factors affecting progression free survival for multiple myeloma patients receiving lenalidomide maintenance after autologous transplantation. Follow-up analysis of the IFM 2005-02 trial</p> <p>Attal M, Lauwers-Cances V, Marit G et al., Maintenance treatment with lenalidomide after transplantation for MYELOMA: Final analysis of the IFM 2005-02</p>  | <p>American Society of Hematology, ASH;122 (406) Blood 2013. Conference: 55th Annual Meeting of the American Society of Hematology, ASH. 122 (21) Blood 2010. Conference: 52nd Annual Meeting of the American Society of Hematology, ASH; 116 (21)</p>   |
| <p>GIMEMA</p> <p>NCT00551928</p>        | <p>Palumbo A, Cavallo F, Gay F et al. Autologous Transplantation and Maintenance Therapy in Multiple Myeloma</p> <p>Boccadoro M, Cavallo F, Gay F et al. Melphalan/prednisone/lenalidomide (MPR) versus high-dose melphalan and autologous transplantation (MEL200) plus lenalidomide maintenance or no maintenance in newly diagnosed multiple myeloma (MM) patients</p> <p>Cavallo F, Gay F, Di Raimondo F, et al. Lenalidomide maintenance improves survival in newly diagnosed young multiple myeloma (MM) patients</p> <p>Cavallo F, Hardan I, Gay F et al., Lenalidomide maintenance significantly reduces the risk of progression in newly diagnosed young multiple myeloma patients enrolled in RV-MM-PI-209 trial</p> <p>Palumbo A, Cavallo F, Gay F et al. Melphalan/Prednisone/Lenalidomide (Mpr) Versus High-Dose Melphalan And Autologous Transplantation (Mel200) In Newly Diagnosed Multiple Myeloma (MM) Patients</p> <p>Cavallo F, Gay F, Caravita di toritto T, Lenalidomide Maintenance Improves Progression Free Survival in Newly Diagnosed Young Multiple Myeloma (MM) Patients</p> | <p>N Engl J Med 2014; 310(10):895-905</p> <p>Journal of clinical oncology; 31(15 suppl. 1) ASCO</p> <p>Haematologica 2013; 98:50</p> <p>Haematologica 2012. 97: 472-473 17th Congress of the European Hematology Association</p> <p>Haematologica 2013, 98:96, 18th Congress of the European Hematology Association</p> <p>Clinical Lymphoma, Myeloma and Leukemia 2013. 13. S12014th International Myeloma Workshop</p> |
| <p>Myeloma XI</p> <p>NCT01554852</p>    | <p>Jackson GH, Davies FE, Pawlyn C et al., Lenalidomide Is a Highly Effective Maintenance Therapy in Myeloma Subjects of All Ages; Results of the Phase III Myeloma XI Study</p> <p>Jackson GH, Davies FE, Pawlyn C et al., Lenalidomide Induction and Maintenance Therapy for Transplant Eligible Myeloma Subjects: Results of the Myeloma XI Study'</p> <p>Jones JR, Cairns DA, Sigworth R et al, Myeloma XI Trial for Newly Diagnosed Multiple Myeloma (NDMM); A Report of Second Primary Malignancy (SPM) Rates and the Importance of Review of Reported Cases</p> <p>Jones J, Pawlyn C, Brioli A et al. Myeloma XI trial-second primary malignancy interim report in newly diagnosed multiple myeloma (NDMM) patients</p>  | <p>ASH 58th Annual Meeting and Exposition San Diego, CA December 3-6 2016</p> <p>ASCO conference presentation 2017, abstract 8009</p> <p>Blood 2015. 126 (23):1847</p> <p>Blood 2014 Conference: 56th Annual Meeting of the American Society of Hematology, ASH.124(21)</p>  |
| <p>Thalidomide</p>                      |   |  |
| <p>Myeloma IX</p> <p>ISRCTN68454111</p> | <p>Morgan G, Davies FE, Gregory WM et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis</p> <p>Morgan G, Davies FE, Gregory WM et al. Long-term follow-up of MRC Myeloma IX trial: Survival outcomes with bisphosphonate and thalidomide treatment</p> <p>Morgan G, Davies FE, Gregory WM et al. Thalidomide maintenance</p>  | <p>Blood 2012, 119(1), pp. 7–15</p> <p>Clinical Cancer Research 2013, 19 (21): 6030-6038</p> <p>Blood 2010. Conference:</p>  |

| Trial ID | Protocol title/ Publication title  | Publication citation   |
|----------|--|--|
|          | significantly improves progression-free survival (PFS) and overall survival (OS) of myeloma patients when effective relapse treatments are used: MRC myeloma IX results' | 52nd Annual Meeting of the American Society of Hematology, ASH. 116 (21) |

Source: Table 2.2.1, p.40-42 of the submission.

6.9 The key features of the randomised trials are summarised in the table below.

**Table 3: Key features of the included evidence – direct and indirect comparisons**

| Trial                           | N                | Design/ duration <sup>a</sup>  | Risk of bias    | Patient population | Outcomes                      | Use in modelled evaluation        |
|---------------------------------|------------------|--|-----------------|--------------------|-------------------------------|-----------------------------------|
| <b>Lenalidomide vs. placebo</b> |                  |  |                 |                    |                               |                                   |
| CALGB                           | 460              | R, DB  | Low; cross-over | Post-ASCT          | PFS, OS, ORR, PFS2.           | OS, PFS, AE.                      |
| IFM 2005-02                     | 614              | R, DB  | Low             | Post-ASCT          | PFS, OS, ORR, PFS2.           | OS, PFS sensitivity analysis, AE. |
| GIMEMA                          | 135 <sup>b</sup> | R, OL  | Low/unclear     | ASCT and non-ASCT  | PFS, OS, PFS2.                | OS, PFS sensitivity analysis, AE. |
| Myeloma XI                      | 788 <sup>b</sup> | R, OL, ongoing   | Low/unclear     | ASCT and non-ASCT  | PFS                           | PFS sensitivity analysis          |
| Meta-analysis                   |                  | Included CALGB (adjusted for cross-over), IFM 2005-02, GIMEMA (subgroup analysis) and Myeloma XI (subgroup analysis) assessed PFS. Included CALGB (adjusted for cross over), IFM 2005 02 and GIMEMA (subgroup analysis) assessed OS. |                 |                    |                               | OS and PFS, sensitivity analysis  |
| <b>Thalidomide vs. BSC</b>      |                  |  |                 |                    |                               |                                   |
| Myeloma IX                      | 493 <sup>b</sup> | R, OL  | Low/unclear     | ASCT and non-ASCT  | PFS, OS (partially reported). | OS (estimated), PFS               |
| MM6                             | 243              | R, OL  | Low             | Post-ASCT          | PFS, OS                       | Not used                          |

Abbreviations: AE = adverse events; ASCT = autologous stem cell transplant; DB = double blind; OL = open label; OS = overall survival; PFS = progression-free survival; PFS2 = progression free survival after next line of therapy; R = randomised.

Note: a. duration of use until progression or intolerance/significant AEs.

b. Reported subgroup only, Total population as follows: GIMEMA = 273; Myeloma XI = 1,550 and Myeloma IX= 820.

Source: Table 2.3.1, p.51-54 and Table 2.3.2, p.56-57 of the submission. Section 2.5-2.6, p.80-127 of the submission. MM6 from Spencer 2009 and Kalf 2014.

6.10 In CALGB, cross-over occurred from the placebo arm to the lenalidomide arm after the study was unblinded following the interim analysis. Cross-over was only allowed for placebo patients who had not progressed. The ESC noted that comparative efficacy based on PFS and OS outcomes may be diluted by cross-over, biasing against lenalidomide, and while the submission adjusted for this effect, the ESC considered that this made interpretation of long-term survival difficult.

6.11 The IFM 2005-02 study was unblinded following the interim analysis (July 2010). However, cross-over by placebo patients to lenalidomide prior to progression was not allowed. Following a subsequent interim analysis (January 2011) all patients remaining in the lenalidomide group (38%) were discontinued due to a higher number of second primary malignancies (SPM).

6.12 The included trials differed with regard to the type of induction therapy prior to ASCT. The proportion of use of lenalidomide as induction therapy differed across the trials as follows: CALGB (34%), IFM 2005-02 (0%), GIMEMA (100%), Myeloma IX (not

reported) and Myeloma XI (51%). Currently, only bortezomib or thalidomide, but not lenalidomide, are available on the Australian PBS for induction therapy for transplant eligible patients with NDMM. Therefore, the use of lenalidomide as induction in CALGB (34%), GIMEMA (100%) and Myeloma XI (51%) represents an applicability issue between the trials and the Australian setting.

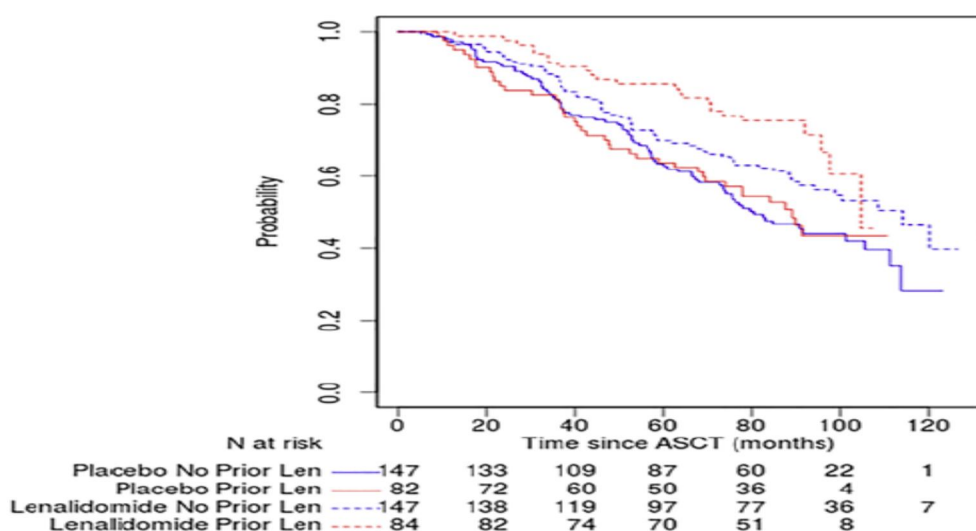
- 6.13 A meta-analysis (McCarthy 2017; CALGB, IFM 2005-02 and GIMEMA) found that the use of lenalidomide induction therapy compared to alternative induction therapy in subjects undergoing lenalidomide maintenance conferred a statistically significant OS benefit with an HR = 0.50 (95% CI: 0.32 to 0.77). However, a published analysis of the CALGB study<sup>3</sup> presented in the PSCR (p5) found that there was improved OS with lenalidomide maintenance regardless of whether or not patients had received previous induction with lenalidomide, and the median OS did not differ significantly between patients who received lenalidomide induction (104.7 months 95% CI 97.8, not reached) and those who did not receive lenalidomide induction (113.8 months; 95% CI 90.5, not reached; hazard ratio [HR] 0.66, 95% CI 0.41, 1.05; p=0.078). For patients in the placebo group, the presence or absence of lenalidomide induction did not affect the median time to disease progression (HR 0.84; 95% CI 0.62, 1.15) or OS (HR 0.97; 95% CI 0.67, 1.42; appendix p11).
- 6.14 The PBAC noted that while there was evidence of benefit from lenalidomide maintenance therapy regardless of induction therapy used, there was some evidence of greater benefit in patients who had received lenalidomide induction therapy. As lenalidomide induction therapy for transplant-eligible patients is not currently available through the PBS, this could indicate that the benefit of lenalidomide maintenance may be overestimated compared to the expected Australian population.

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<sup>3</sup> Holstein, SA, Jung, SH, Richardson, PG, Hofmeister, CC, Hurd, DD, Hassoun, H, et al. (2017). "Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial." *Lancet Haematol* 4(9): e431-e442.

Figure 1 Overall survival in CALGB: patients with and without prior lenalidomide induction

B



6.15 There were transitivity issues between the trials for lenalidomide. IFM 2005-02, GIMEMA and Myeloma XI used different lenalidomide dosing regimens compared to the CALGB trial, which used a starting dose of 10 mg/day for each day of the 28-day cycle, with dose escalation after 3 months to 15 mg/day if tolerated. Subjects in both arms of IFM 2005-02 received 2 cycles of 25 mg/day lenalidomide post-ASCT, followed by 10 mg/day, with subjects in IFM 2005-02 able to increase to 15 mg/day after 3 months. Both GIMEMA and Myeloma XI used daily dosing for 21 days/28 day cycle; at 10 mg/day for GIMEMA and Myeloma XI. This also poses applicability issues for these trials with respect to the dosing requested for use in the Australian setting (daily dosing of 10 mg up to 15 mg per day in 28-day cycles). Accordingly, these trials were included in the indirect comparison as a sensitivity analysis.

## Comparative effectiveness

### Lenalidomide vs. BSC

6.16 The PFS and OS results from CALGB and IFM 2005-02 are presented in Tables 4 and 5 (with the corresponding Kaplan-Meier data in Figures 1 and 2). While both trials showed a statistically significant improvement in PFS, only CALGB showed a statistically significant improvement in OS. The submission argued that this was due to the IFM 2005-02 trial being underpowered to detect a difference in OS. Additionally, the trial was unblinded after the interim analysis (July 2010) allowing for early stopping of treatment. The submission argued that subjects randomised to placebo may have started second-line anti-myeloma therapy prior to progression which may dilute the treatment effect for lenalidomide with respect to OS (p.87 of the submission).

**Table 4: PFS results – lenalidomide versus best supportive care**

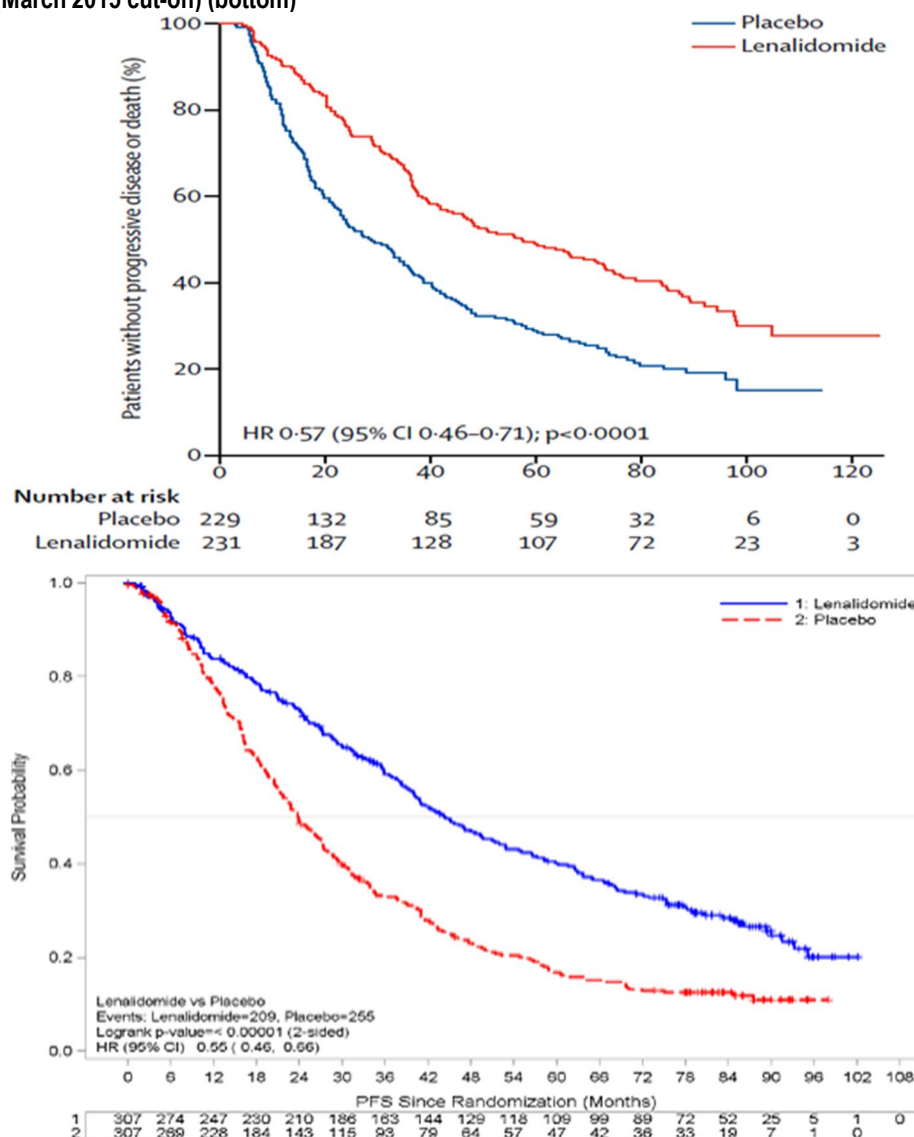
| Trial ID              | Lenalidomide    |                           | BSC             |                           | Difference in median, months | P value (log rank test) | Hazard ratio (95% CI)    |
|-----------------------|-----------------|---------------------------|-----------------|---------------------------|------------------------------|-------------------------|--------------------------|
|                       | n/N event (%)   | Median PFS, mths (95% CI) | n/N event (%)   | Median PFS, mths (95% CI) |                              |                         |                          |
| CALGB                 |                 |                           |                 |                           |                              |                         |                          |
| Oct 2016 <sup>a</sup> | 146/231 (63%)   | 57.3 (44.2, 73.3)         | 176/229 (77%)   | 28.9 (23.0, 36.3)         | 28.4                         | p<0.001                 | <b>0.57 (0.46, 0.71)</b> |
| IFM 2005-02           |                 |                           |                 |                           |                              |                         |                          |
| Feb 2016 <sup>b</sup> | 218/307 (71.0%) | 44.4 (39.6, 52.0)         | 257/307 (83.7%) | 23.8 (21.2, 27.3)         | 20.6                         | p< 0.001                | <b>0.57 (0.47, 0.68)</b> |

Abbreviations: BSC=best supportive care; CI= confidence interval; n= number of participants reporting data; N= total participants in group; NE= not evaluable.

Notes: a from ASCT; b from maintenance randomisation. Statistically significant differences bolded.

Source: Table 2.5.1, p.80 of the submission.

**Figure 2: Kaplan-Meier curves of PFS comparing lenalidomide with BSC (CALGB (Oct 2016 cut-off) top) IFM 2005-02 (March 2015 cut-off) (bottom)**



Abbreviations: ASCT = autologous stem cell transplant; CI = confidence interval; HR = hazard ratio; PFS = progression-free survival  
 Notes: For CALGB, PFS was measured as time since ASCT according to EMA censoring rules (months); For IFM, PFS was measured as time since maintenance randomisation to EMA censored progression (months). Trial refers to placebo, have used best supportive care for

consistency.

Source: CALGB, Figure 2.5.1, p.82 of the submission; IFM, Figure 2.5.2, p.84 of the submission.

**Table 5: OS results – lenalidomide versus BSC**

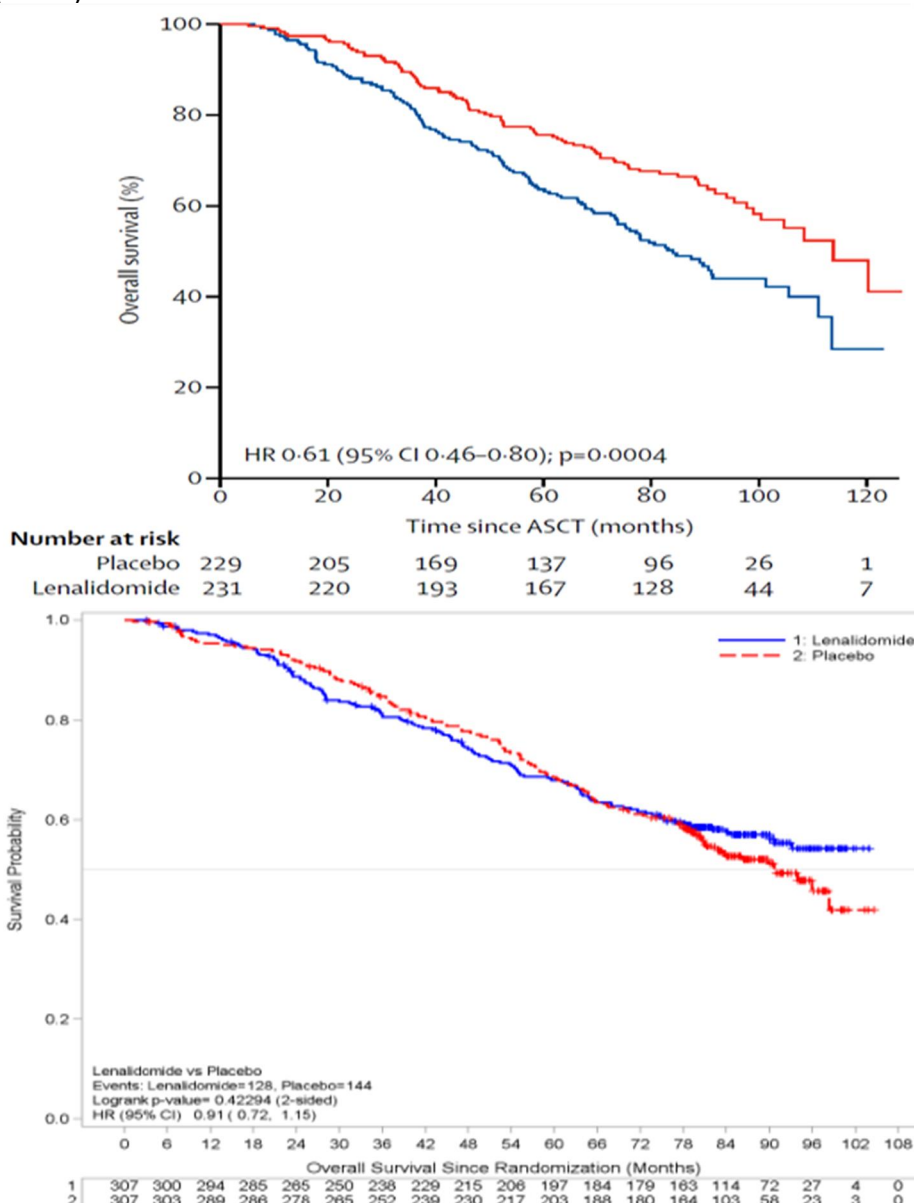
| Trial ID              | Lenalidomide    |                          | BSC              |                         | Difference in median, months | P value (log rank test) | Hazard ratio (95% CI)    |
|-----------------------|-----------------|--------------------------|------------------|-------------------------|------------------------------|-------------------------|--------------------------|
|                       | n/N event (%)   | Median OS, mths (95% CI) | n/N event (%)    | Median OS mths (95% CI) |                              |                         |                          |
| CALGB                 |                 |                          |                  |                         |                              |                         |                          |
| Oct 2016 <sup>a</sup> | 88/231 (38.1%)  | 113.8 (100.4, NE)        | 120/229 (52.4%)  | 84.1 (73.8, 106.0)      | 29.7                         | p=0.0004                | <b>0.61 (0.46, 0.80)</b> |
| IFM 2005-02           |                 |                          |                  |                         |                              |                         |                          |
| Feb 2016 <sup>b</sup> | 143/307 (46.6%) | 105.9 (88.8, NE)         | 160/307* (52.1%) | 88.1 (80.7, 108.4)      | 17.8                         | p=0.355                 | 0.90 (0.72, 1.13)        |

Abbreviations: ASCT= autologous stem cell transplant; BSC=best supportive care; CI = confidence interval; n = number of participants with event; N = total participants in arm; NA = not available (not reported); NE = not evaluable; NR = not reached; OS = overall survival.

Notes: Myeloma XI: OS has not been reported; Myeloma IX: post-ASCT pathway, the median OS was not reached in either arm and the HR not reported. a from ASCT; b from maintenance randomisation. \*Figures corrected from submission and proportions presented to 1 decimal point. Statistically significant differences bolded.

Source: Table 2.5.3, p.85-86 of the submission.

Figure 3: Kaplan-Meier curve of OS of lenalidomide compared with BSC CALGB (Oct 2016 cut-off) (top) IFM 2005-02 (bottom)



Abbreviations: ASCT= autologous stem cell transplant; CI= confidence interval; HR= hazard ratio; OS= overall survival.

Notes: For CALGB, OS is measured as time since ASCT (months); for IFM, OS is measured as time since maintenance randomisation (months). Trial refers to placebo, have used best supportive care for consistency.

Source: CALGB, Figure 2.5.4, p.86 of the submission; IFM 2005-02, Figure 2.5.5, p.87 of the submission.

6.17 The results for the post-ASCT subgroups in GIMEMA (PFS and OS) and Myeloma XI (PFS) were also presented by the submission. However, both GIMEMA and Myeloma XI used daily dosing for 21 days/28 day cycle; at 10 mg/day. The GIMEMA and Myeloma XI included NDMM patients who did not receive an ASCT but were randomised to maintenance therapy; the submission relied on subgroups of patients who received maintenance therapy post-ASCT from the trials; none of these trials were powered to detect a difference in treatment effect in the post-ASCT subgroup.

The GIMEMA and Myeloma XI trials reported a significant improvement in PFS, HR 0.42 (95%CI 0.24, 0.73) and 0.47 (95%CI 0.38, 0.52) respectively in the post-ASCT subgroup. This was not significantly different to the complement groups in either trial (HR 0.43 95%CI 0.28, 0.67; and 0.42 95%CI 0.35, 0.51, respectively). The ESC noted that there were no statistically significant improvements in OS with lenalidomide versus BSC in the post-ASCT subgroup in GIMEMA (HR 0.62 95% CI 0.24, 1.59) or the complement (HR 0.68 95%CI 0.32, 1.45; test for interaction  $p=0.89$ ). The PBAC noted that updated results were presented for Myeloma XI at the 2017 American Society of Hematology conference, which showed consistent PFS outcomes to those reported in submission and a significant improvement in OS, however these results are yet to be published in full.<sup>4</sup>

#### Lenalidomide vs. BSC network meta-analysis

- 6.18 A network meta-analysis was commissioned for the submission using the most recent data available for CALGB, IFM 2005-02, GIMEMA and Myeloma XI. Because of the transitivity issues between CALGB, IFM 2005 02, GIMEMA and Myeloma XI with respect to the lenalidomide dosing regimen and use of lenalidomide as induction therapy, the ESC considered that it was inappropriate to conduct a meta-analysis of these studies. The PBAC noted this cautionary advice but considered it preferable and appropriate to also consider the totality of the evidence rather than rely on evidence from one trial.
- 6.19 The submission relied on the effectiveness data from the CALGB trial in the economic evaluation and presented a sensitivity analysis using the treatment effect from the meta-analysis.
- 6.20 The submission applied four analysis methods to account for cross-over effects in OS and PFS in CALGB. These were ITT, censoring subjects at time of cross-over (per protocol approach), rank preserving structural failure time model (RPSFTM); and iterative parameter estimation (IPE) algorithm. The adjusted PFS and OS using the RPSFTM were used in the indirect comparison to thalidomide. Application of the RPSFTM was consistent with the IPE for PFS and OS. The meta-analysis of CALGB, IFM 2005-02 and GIMEMA for OS was subject to a high degree of heterogeneity. Three of the analysis methods showed a statistically significant difference in favour of lenalidomide, while the fourth (which adjusted for cross-over in CALGB and adopted a random effects approach) resulted in a 95% CI for the HR that crossed 1. The ESC considered that if a network meta-analysis approach were to be taken, given the heterogeneity between the trials, a random effects model should be used. The PBAC noted that using the model preferred by ESC, this resulted in a non-significant improvement in OS after adjusting for cross-over.

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<sup>4</sup> Lenalidomide Maintenance Significantly Improves Outcomes Compared to Observation Irrespective of Cytogenetic Risk: Results of the Myeloma XI Trial <https://ash.confex.com/ash/2017/webprogram/Paper102882.html>

**Table 11: Results of the network meta-analyses of lenalidomide studies**

| Measurement                  | Outcome (LEN vs PBO/BSC) HR (95% CI) <sup>b</sup>                   | Survival time, months Median (95% CI) | Heterogeneity         | Studies                                |
|------------------------------|---|---------------------------------------|-----------------------|--|
| PFS <sup>c</sup>             | Fixed effects 0.55 (0.49, 0.62)<br>Random effects 0.55 (0.49, 0.62) | NR                                    | I <sup>2</sup> =0%    | CALGB, IFM 2005-02, GIMEMA, Myeloma XI |
| PFS (Adjusted) <sup>cd</sup> | Fixed effects 0.53 (0.46, 0.59)<br>Random effects 0.53 (0.46, 0.59) | NR                                    | I <sup>2</sup> =0%    |  |
| OS                           | Fixed effects 0.76 (0.64, 0.90)<br>Random effects 0.73 (0.55,0.99)  | NR                                    | I <sup>2</sup> =56.6% | CALGB, IFM 2005-02, GIMEMA             |
| OS (Adjusted) <sup>d</sup>   | Fixed effects 0.75 (0.63, 0.90)<br>Random effects 0.68 (0.45,1.04)  | NR                                    | I <sup>2</sup> =72.9% |  |

Source: Table 2.6.3, p.113-114 of the submission.

Abbreviations: AMT=anti-myeloma treatment; BSC=best supportive care; CI=confidence interval; EMA=European Medicines Agency; FDA=Federal Drug Administration; HR=hazard ratio; ITT=intention to treat; LEN=lenalidomide; NMA=network meta-analysis; NR=not reported; OS=overall survival; PFS=progression-free survival; PFS2= progression-free survival after next therapy; PD=progressive disease; RPSFTM = rank preserving structural failure time model. Notes: a There are some differences between McCarthy 2017 meta-analysis and the Celgene OS meta-analysis report in terms of OS at March 2015. Primary differences appear to be due to a smaller number of subjects used by McCarthy 2017 in the PBO/OBS arm (N=67 in McCarthy vs N=68 OS meta-analysis report) due to one person developing PD during consolidation being excluded by McCarthy 2017. Thus there were 491 deaths in OS meta-analysis report and 490 deaths in McCarthy 2017). b Feb 2016 data cut used for CALGB, IFM 2005-02 and GIMEMA, except for CALGB OS (ITT) results which used the Oct 2016 data cut. Myeloma XI results are from Jackson 2016. c. EMA censoring was used for CALGB, IFM 2005 02 and GIMEMA and censoring rules were not reported for Myeloma XI d. CALGB results adjusted for cross-over using RPSFTM.

### Thalidomide vs. BSC

6.21 The PFS and OS results for the post-ASCT subgroup in Myeloma IX are presented in Tables 8 and 9. No Kaplan-Meier curves were presented for the post-ASCT subgroup in Myeloma IX. There was a statistically significant improvement for the post-ASCT subgroup for PFS but not for OS in Myeloma IX.

**Table 8: Results of post-ASCT subgroup analysis– PFS -thalidomide versus BSC**

| Trial ID                  | Thalidomide   |                           | BSC           |                           | Difference in median, months | P-value | Hazard ratio (95% CI)    | P-value for interaction |
|---------------------------|---------------|---------------------------|---------------|---------------------------|------------------------------|---------|--------------------------|-------------------------|
|                           | n/N event (%) | Median PFS, mths (95% CI) | n/N event (%) | Median PFS, mths (95% CI) |                              |         |                          |                         |
| Myeloma IX (October 2009) |               |                           |               |                           |                              |         |                          |                         |
| Whole                     | NR            | 23 (NR)                   | NR            | 15 (NR)                   | 8                            | p<0.001 | <b>0.69 (0.58, 0.82)</b> | NA                      |
| ASCT                      | NR            | 30 (NR)                   | NR            | 23 (NR)                   | 7                            | p=0.003 | <b>0.70 (0.56, 0.88)</b> | NR                      |
| Complement                | NR            | 11 (NR)                   | NR            | 9 (NR)                    | 2                            | p=0.014 | <b>0.74 (0.58, 0.94)</b> |                         |

Abbreviations: ASCT= autologous stem cell transplant; BSC=best supportive care; CI=confidence interval; n=number of participants reporting data; N=total participants in group; NA=not applicable; NE= not evaluable; NR = not reported

Notes: Updated results for Myeloma IX for data cut-off 5 Jan 2012 show PFS remains unchanged with additional follow-up data for the whole trial population (update not available by pathway) median PFS in thalidomide and OBS was 22 months vs. 15 months HR for PFS 0.69 (95% ci: 0.59, 0.82). Inverse HR reported in submission. Statistically significant differences bolded.

Source: Table 2.5.1, p.80 and Table 2.6.1, p.108 of the submission. Figure 2.6.1, p.109 of the submission. p.10 Morgan 2012.

**Table 9: Results of subgroup analysis – OS – thalidomide versus BSC**

| Trial ID                  | Thalidomide        |                          | BSC                |                          | Difference in median, months | P-value | Hazard ratio (95% CI) | P-value for interaction |
|---------------------------|--------------------|--------------------------|--------------------|--------------------------|------------------------------|---------|-----------------------|-------------------------|
|                           | n/N with event (%) | Median OS, mths (95% CI) | n/N with event (%) | Median OS, mths (95% CI) |                              |         |                       |                         |
| Myeloma IX (October 2009) |                    |                          |                    |                          |                              |         |                       |                         |
| Whole                     | NR                 | NR                       | NR                 | NR                       | NR                           | p=0.40  | 1.10 (0.85, 1.35)     | NA                      |
| ASCT                      | NR                 | NR (3-yr OS 75%)         | NR                 | NR (3-yr OS 80%)         | NR                           | p=0.26  | NR                    | NR.                     |
| Complement                | NR                 | 38                       | NR                 | 39                       | -1                           | p=0.995 | 1.00 (0.72, 1.37)     |                         |

Abbreviations: ASCT= autologous stem cell transplant; BSC=best supportive care; NA=not applicable; NR=not reported; OS=overall survival.

Note: At most recent data cut (Jan 2012), there was no evidence of a difference in OS for the whole trial (both ASCT and no ASCT pathways combined; p=0.70) with median OS of 60 months with thalidomide maintenance and observation. Inverse HR reported in submission.

Source: Table 2.5.2 p.85 and Table 2.6.2, p.110 of the submission. P.10, Morgan 2012.

- 6.22 The PFS and OS results for the MM6 and Myeloma X thalidomide trials (all post-ASCT), which were not presented in the submission, are summarised in Table 10 (and Figure 4 for MM6). Thalidomide was associated with statistically significant improvements in PFS in both trials, but a statistically significant improvement in OS was only demonstrated in MM6. Failing to include MM6 potentially resulted in the OS benefit with thalidomide being underestimated.
- 6.23 The PSCR argued that the exclusion of MM6 was reasonable on the basis that it was investigating consolidation treatment and used an active comparator arm. The ESC considered that with a starting and median dose of thalidomide in the trial of 100 mg, and treatment duration of up to 12 months, the setting was largely consistent with the current recommendation of the MSAG guidelines for maintenance treatment. The ESC also considered that alternate days of prednisolone is a treatment approach currently used as best supportive care and noted that this was consistent with the statement in the PSCR (p1) that best supportive care included all therapies other than lenalidomide and thalidomide. The ESC further noted that inclusion of an active comparator treatment in the thalidomide trial biased the comparison of lenalidomide versus thalidomide in favour of lenalidomide.
- 6.24 The PBAC agreed with ESC that the MM6 was a relevant trial of an alternative maintenance treatment. However, the PBAC noted that the MM6 trial was conducted during an earlier time period compared with the trials presented for lenalidomide maintenance, and considered that substantial changes in patient care over this time, and in particular in the induction regimens used, complicate the interpretation of the comparison.

Table 10: Summary of survival outcomes in MM6 and Myeloma X

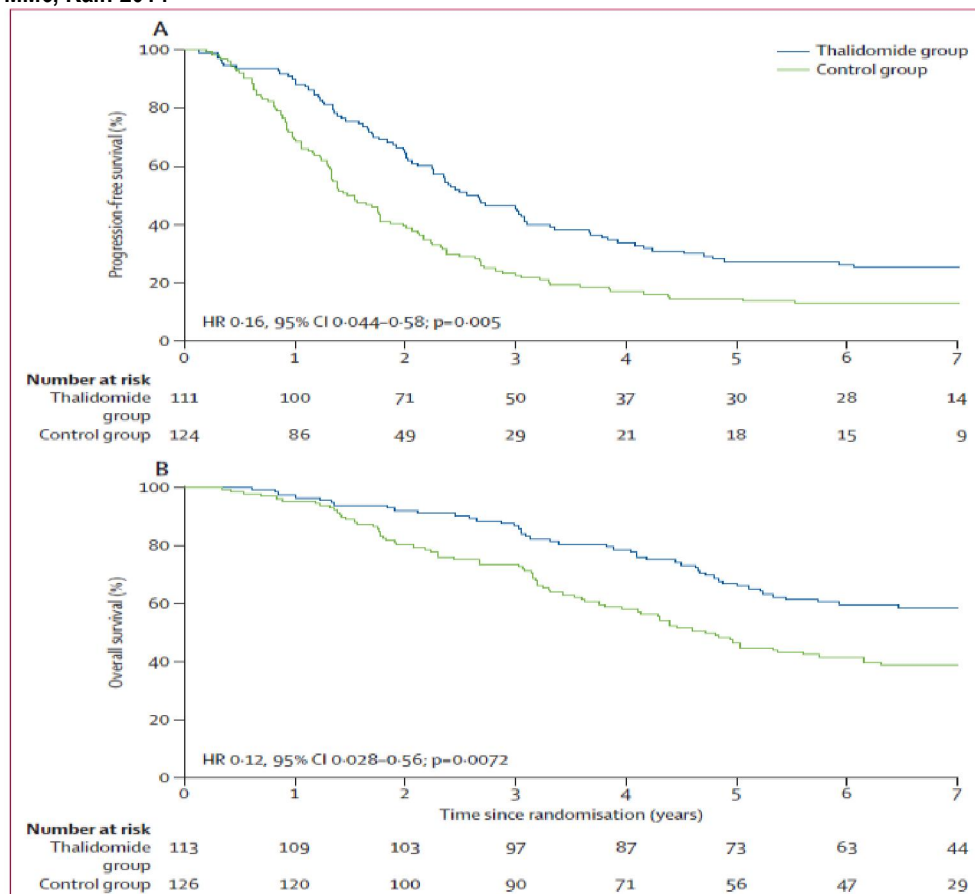
|                                  | THAL                | BSC                | Absolute difference | HR (95% CI)                          |
|----------------------------------|---------------------|--------------------|---------------------|--------------------------------------|
| <b>MM6</b>                       |                     |                    |                     |                                      |
| <b>Progression-free survival</b> |                     |                    |                     |                                      |
| 3-year follow-up                 |                     |                    |                     |                                      |
| Patients with event n/N (%)      | 42%                 | 23%                | 19%                 | -                                    |
| Median PFS months (95% CI)       | 30.6 (26.9, 40.1)   | 18.4 (15.8, 24.1)  | 12.2                | <b>0.50 (0.35, 0.71); p&lt;0.001</b> |
| 5.4-year follow-up               |                     |                    |                     |                                      |
| Patient with event n/N (%)       | -                   | -                  | -                   | -                                    |
| Median PFS months (95% CI)       | 32.4 (25.2, 38.4)   | 18.0 (13.2, 21.6)  | 14.4                | <b>0.16 (0.04, 0.58); p=0.005</b>    |
| <b>Overall survival</b>          |                     |                    |                     |                                      |
| 3-year follow-up                 |                     |                    |                     |                                      |
| Patients with event n/N (%)      | 86%                 | 75%                | 11%                 | -                                    |
| Median OS months (95% CI)        | -                   | -                  | -                   | <b>0.41 (0.22,0.76), p=0.004</b>     |
| 5.4-year follow-up               |                     |                    |                     |                                      |
| Patients with event              | -                   | -                  | -                   | -                                    |
| Median months OS (95% CI)        | 102.0 (88.8, 116.4) | 54.0 (46.8, 61.2)  | 48.0                | <b>0.12 (0.028, 0.56), p=0.0072</b>  |
| <b>Myeloma X</b>                 |                     |                    |                     |                                      |
| <b>Progression-free survival</b> |                     |                    |                     |                                      |
| 4.1-year follow-up               |                     |                    |                     |                                      |
| Patients with event n/N (%)      | 4-yr estimates 32%  | 4-yr estimates 14% | -                   | -                                    |
| Median PFS months (95% CI)       | -                   | -                  | -                   | <b>0.56 (NR,NR); p&lt;0.0001</b>     |
| <b>Overall survival</b>          |                     |                    |                     |                                      |
| 4.1-year follow-up               |                     |                    |                     |                                      |
| Patients with event n/N (%)      | 4-yr estimates 68%  | 4-yr estimates 60% | -                   | -                                    |
| Median OS months (95% CI)        | NE                  | NE                 | -                   | <b>0.77 (0.53, 1.14);p=0.18</b>      |

Abbreviations: CI=confidence interval; HR=hazard ratio; LEN=lenalidomide, PF=progression free survival; NE=not evaluable; OS=overall survival.

Note: Spencer 2009 reported median PFS in days, this was converted into months. Kalf 2014 reported median PFS and OS in years, this was converted into months. Median follow-up in Kalf et al. 2014 was 5.4 years (IQR 3.1-7.2). Median follow-up in Spencer 2009 was approx. 3 years. Statistically significant differences bolded.

Source: MM6 from Spencer 2009 and Kalf 2014. Myeloma X from Stewart 2013.

Figure 4: Kaplan-Meier curves showing progression-free survival (A) and overall survival (B) by treatment group in MM6, Kalfi 2014



Note: 5.4 year follow-up

Source: Figure 2, p115, Kalfi 2014.

### Lenalidomide vs. thalidomide indirect comparison

6.25 The results of the indirect comparison of CALGB and Myeloma IX for PFS and OS are presented in Tables 12 and 13. The submission applied an HR for OS in Myeloma IX of 1.29, estimated based on the proportion alive at 3 years from the October 2009 data cut-off (thalidomide 75% vs observation 80%, p=0.26) and assuming an exponential distribution for survival. Applying this estimated HR in the indirect comparison resulted in superior OS for lenalidomide compared with thalidomide that flowed through to the economic evaluation. The ESC agreed with the evaluation that the outcome of superior OS may not be supported if the results for thalidomide from MM6 (which showed thalidomide resulted in a survival gain compared with BSC) were included in the indirect comparison. The indirect comparison concluded that lenalidomide was non-inferior to thalidomide for PFS and superior for OS. The PBAC considered that it was implausible that lenalidomide could confer an OS benefit without also conferring a PFS benefit.

**Table 12: Results of the indirect comparison for PFS – base case**

|   | Outcome           | Lenalidomide<br>n/N (%) | BSC<br>n/N (%)    | Absolute<br>difference | HR (95% CI)               |
|---|-------------------|-------------------------|-------------------|------------------------|---------------------------|
| CALGB (Adj -<br>RPSFTM)   | Progressed        | NR                      | NR                | -                      | -                         |
|   | Median months PFS | 56.9 (22.1, NE)         | 25.8 (10.9, 66.1) | 31.1 mths*             | <b>0.52 (0.39, 0.69)</b>  |
| CALGB (ITT)   | Progressed        | NR                      | NR                | -                      | -                         |
|   | Median months PFS | 56.9 (41.9, 71.7)       | 29.4 (20.7, 35.5) | 27.5 mths              | <b>0.61 (0.48, 0.76)*</b> |
| Comparators   |                   | Thalidomide<br>n/N (%)  | BSC<br>n/N (%)    | Absolute<br>difference | HR (95% CI)               |
| Myeloma IX  | Progressed        | NR                      | NR                | -                      | -                         |
|   | Median months PFS | 30 (NR)                 | 23 (NR)           | 7 mths                 | <b>0.70 (0.56, 0.88)</b>  |
| <b>Indirect comparison lenalidomide (CALGB adj) vs. thalidomide (base case)</b> |                   |                         |                   |                        | 0.74 (0.52, 1.07)         |
| <b>Indirect comparison lenalidomide (CALGB ITT) vs. thalidomide</b>             |                   |                         |                   |                        | 0.87 (0.63, 1.20)         |

Abbreviations: BSC=best supportive care; ITT=intention to treat; HR=hazard ratio; NE=not evaluable; NR=not reported; PFS=progression free survival; RPSFTM = rank preserving structural failure time model.

Note: fixed effects used for PFS. Base case CALGB (February 2016) estimate adjusted for cross-over using RPSFTM. Statistically significant differences bolded.

\* calculated during the evaluation (56.9-25.8 = 31.1)

Source: Table 2.6.5, p.120 of the submission. Table 2.5.1, p.80 of the submission.

**Table 13: Results of the indirect comparison for OS – base case**

|   | Outcome          | Lenalidomide<br>n/N (%) | BSC<br>n/N (%)     | Absolute<br>difference | HR (95% CI)              |
|---|------------------|-------------------------|--------------------|------------------------|--------------------------|
| CALGB (Adj -<br>RPSFTM)   | Death            | NR                      | NR                 | -                      | -                        |
|   | Median months OS | 111.0 (59.4, NE)        | 72.2 (34.6, 110.7) | 38.8 mths*             | <b>0.51 (0.37, 0.74)</b> |
| CALGB (ITT)   | Death            | 88/231 (38%)            | NR                 | -                      | -                        |
|   | Median months OS | 113.8 (100.4, NE)       | 84.1 (73.8, 106.0) | 29.7 mths              | <b>0.61 (0.46, 0.80)</b> |
| Comparators   |                  | Thalidomide<br>n/N (%)  | BSC<br>n/N (%)     | Absolute<br>difference | HR (95% CI)              |
| Myeloma IX  | Death            | NR                      | NR                 | -                      | -                        |
|   | Median months OS | NR                      | NR                 | -                      | 1.29 <sup>a</sup>        |
| <b>Indirect comparison lenalidomide (CALGB adj) vs. thalidomide (base case)</b> |                  |                         |                    |                        | <b>0.40 (0.24, 0.66)</b> |
| <b>Indirect comparison lenalidomide (CALGB ITT) vs. thalidomide</b>             |                  |                         |                    |                        | <b>0.48 (0.29, 0.76)</b> |

Abbreviations: BSC=best supportive care; ITT=intention to treat=HR, hazard ratio; NE=not evaluable; NR=not reported; PFS=progression free survival; RPSFTM = rank preserving structural failure time model.

Note: fixed effects used for PFS. Base case CALGB (February 2016) estimate adjusted for cross-over using RPSFTM. Statistically significant differences bolded. \* calculated during the evaluation (111.0-72.2 = 38.8). a. Estimated based on the proportion alive at 3 – years from the October 2009 data cut-off (thalidomide 75% vs observation 80%, p=0.26) assuming exponential distribution.

Source: Table 2.6.5, p.120 of the submission. Table 2.5.1, p.80 of the submission. Morgan 2012.

6.26 The ESC considered that due to the exclusion of MM6, the indirect comparison presented in the submission may not provide an accurate representation of comparative efficacy between lenalidomide and thalidomide. A naïve indirect comparison of the CALGB, IFM 2005-02, MM6 and Myeloma X trials is presented in tables 14 and 15 below. The ESC noted that the outcomes in the BSC arm of the MM6 trial were considerably worse than in the BSC arm in the two lenalidomide trials, but that despite differences in the absolute values, the outcomes indicated a statistically significant improvement for both lenalidomide and thalidomide over BSC of similar proportions. The PBAC considered that the difference in absolute values was likely due, at least in part, to improvements in patient care, including induction therapies, in the time between the MM6 and lenalidomide maintenance trials being conducted. The PBAC also considered that it was relevant that the relative

improvement in PFS and OS were comparable, which indicated that within their respective contexts both thalidomide and lenalidomide had similar benefits over BSC.

- 6.27 The PBAC considered the indirect comparison should be based on all appropriate trials and preferably use more complete data for Myeloma IX, and updated data from Myeloma XI.

**Table 14: PFS results – naïve indirect comparison lenalidomide versus thalidomide**

| Trial ID                                 | Lenalidomide/Thalidomide |                           | BSC             |                           | Difference in median, months | P value  | Hazard ratio (95% CI)    |
|--|--------------------------|---------------------------|-----------------|---------------------------|------------------------------|----------|--------------------------|
|  | n/N event (%)            | Median PFS, mths (95% CI) | n/N event (%)   | Median PFS, mths (95% CI) |                              |          |                          |
| Lenalidomide vs. BSC                     |                          |                           |                 |                           |                              |          |                          |
| CALGB Oct 2016 <sup>a</sup>              | 146/231 (63%)            | 57.3 (44.2, 73.3)         | 176/229 (77%)   | 28.9 (23.0, 36.3)         | 28.4                         | p<0.001  | <b>0.57 (0.46, 0.71)</b> |
| IFM 2005-02 Feb 2016 <sup>b</sup>        | 218/307 (71.0%)          | 44.4 (39.6, 52.0)         | 257/307 (83.7%) | 23.8 (21.2, 27.3)         | 20.6                         | p< 0.001 | <b>0.57 (0.47, 0.68)</b> |
| Thalidomide vs BSC                       |                          |                           |                 |                           |                              |          |                          |
| MM6 5.4 year follow-up                   | -                        | 32.4 (25.2, 38.4)         | -               | 18.0 (13.2, 21.6)         | 14.4                         | p=0.005  | <b>0.16 (0.04, 0.58)</b> |
| Myeloma IX (October 2009) ASCT sub-group | NR                       | 30 (NR)                   | NR              | 23 (NR)                   | 7                            | p=0.003  | <b>0.70 (0.56, 0.88)</b> |

Abbreviations: BSC=best supportive care; CI= confidence interval; n= number of participants reporting data; N= total participants in group; NE= not evaluable.

Notes: a from ASCT; b from maintenance randomisation. Note: Spencer 2009 reported median PFS in days, this was converted into months. Kalfi 2014 reported median PFS and OS in years, this was converted into months. Median follow-up in Kalfi et al. 2014 was 5.4 years (IQR 3.1-7.2). Median follow-up in Spencer 2009 was approx. 3 years. Statistically significant differences bolded.

Source: MM6 from Spencer 2009 and Kalfi 2014. Myeloma X from Stewart 2013. Table 2.5.1, p.80 of the submission.

**Table 15: OS results – naïve indirect comparison lenalidomide vs. thalidomide**

| Trial ID                                     | Lenalidomide/Thalidomide |                          | BSC               |                         | Difference in median, months | P value (log rank test) | Hazard ratio (95% CI)     |
|--|--------------------------|--------------------------|-------------------|-------------------------|------------------------------|-------------------------|---------------------------|
|  | n/N event (%)            | Median OS, mths (95% CI) | n/N event (%)     | Median OS mths (95% CI) |                              |                         |                           |
| Lenalidomide vs. BSC                         |                          |                          |                   |                         |                              |                         |                           |
| CALGB Oct 2016 <sup>a</sup>                  | 88/231 (38.1%)           | 113.8 (100.4, NE)        | 120/229 (52.4%)   | 84.1 (73.8, 106.0)      | 29.7                         | p=0.0004                | <b>0.61 (0.46, 0.80)</b>  |
| IFM 2005-02 Feb 2016 <sup>b</sup>            | 143/307 (46.6%)          | 105.9 (88.8, NE)         | 160//307* (52.1%) | 88.1 (80.7, 108.4)      | 17.8                         | p=0.355                 | 0.90 (0.72, 1.13)         |
| Thalidomide vs BSC                           |                          |                          |                   |                         |                              |                         |                           |
| MM6 5.4 year follow-up                       | -                        | 102.0 (88.8, 116.4)      | -                 | 54.0 (46.8, 61.2)       | 48.0                         | p=0.0072                | <b>0.12 (0.028, 0.56)</b> |
| Myeloma IX (October 2009) Post-ASCT subgroup | NR                       | NR (3-yr OS 75%)         | NR                | NR (3-yr OS 80%)        | NR                           | p=0.26                  | NR                        |

Abbreviations: BSC=best supportive care; CI = confidence interval; n = number of participants with event; N = total participants in arm; NA = not available (not reported); NE = not evaluable; NR = not reached; OS = overall survival.

Notes: a from ASCT; b from maintenance randomisation. \*Figures corrected from submission and proportions presented to 1 decimal point. Spencer 2009 reported median PFS in days, this was converted into months. Kalf 2014 reported median PFS and OS in years, this was converted into months. Median follow-up in Kalf et al. 2014 was 5.4 years (IQR 3.1-7.2). Median follow-up in Spencer 2009 was approx. 3 years. Statistically significant differences bolded.

Source: MM6 from Spencer 2009 and Kalf 2014. Myeloma X from Stewart 2013. Table 2.5.3, p.85-86 of the submission.

## Comparative harms

6.28 A summary of the adverse events (AEs) and occurrence of second primary malignancies (SPMs) in the randomised trials CALGB and IFM 2005-02 is presented in Tables 16 and 17. This shows that the use of lenalidomide compared with placebo is associated with a higher incidence of haematological AEs (neutropenia, leukopenia, thrombocytopenia), infections (lung infection, pneumonia), fatigue and SPMs.

Table 16: Summary of key Grade 3 or 4 treatment-emergent adverse events in the randomised trials

| Trial ID                        | LEN<br>n with<br>event/224 (%) | BSC (to XO)<br>n with<br>event/221(%) | BSC (after<br>XO)<br>n with<br>event/76 (%) | RR (95% CI)                | RD (95% CI)           |
|---------------------------------|--------------------------------|---------------------------------------|---|----------------------------|-----------------------|
| <b>CALGB (March 2015)</b>       |                                |                                       |   |                            |                       |
| Haematological                  |                                |                                       |   |                            |                       |
| Neutropenia                     | 133 (59.4%)                    | 73 (33.0%)                            | 29 (38.2%)                                  | <b>1.80 (1.45, 2.23)</b>   | <b>26% (17%, 35%)</b> |
| Thrombocytopenia                | 84 (37.5%)                     | 67 (30.3%)                            | 9 (11.8%)                                   | 1.24 (0.95, 1.61)          | 7% (-2%, 16%)         |
| Leukopenia                      | 45 (20.1%)                     | 22 (10.0%)                            | 9 (11.8%)                                   | <b>2.02 (1.26, 3.24)</b>   | <b>10% (4%, 17%)</b>  |
| Febrile neutropenia             | 39 (17.4%)                     | 34 (15.4%)                            | 1 (1.3%)                                    | 1.13 (0.74, 1.72)          | 2% (-5%, 9%)          |
| Lymphopenia                     | 37 (16.5%)                     | 26 (11.8%)                            | 5 (6.6%)                                    | 1.40 (0.88, 2.24)          | 5% (-2%, 11%)         |
| Anaemia                         | 23 (10.3%)                     | 18 (8.1%)                             | 2 (2.6%)                                    | 1.26 (0.70, 2.27)          | 2% (-3%, 8%)          |
| Non-haematological              |                                |                                       |   |                            |                       |
| Neutropenic infection           | 27 (12.1%)                     | 14 (6.3%)                             | 5 (6.6%)                                    | 1.90 (1.03, 3.53)          | 6% (0%, 11%)          |
| Lung infection                  | 19 (8.5%)                      | 2 (0.9%)                              | 2 (2.6%)                                    | <b>9.37 (2.21, 39.76)</b>  | <b>8% (4%, 11%)</b>   |
| Pneumonia                       | 15 (6.7%)                      | 4 (1.8%)                              | 1 (1.3%)                                    | <b>3.70 (1.25, 10.97)</b>  | <b>5% (1%, 9%)</b>    |
| Diarrhoea                       | 22 (9.8%)                      | 17 (7.7%)                             | 6 (7.9%)                                    | 1.28 (0.70, 2.34)          | 2% (-3%, 7%)          |
| Nausea                          | 16 (7.1%)                      | 10 (4.5%)                             | 2 (2.6%)                                    | 1.58 (0.73, 3.40)          | 3% (-2%, 7%)          |
| Hypokalaemia                    | 16 (7.1%)                      | 12 (5.4%)                             | 3 (3.9%)                                    | 1.32 (0.64, 2.72)          | 2% (-3%, 6%)          |
| Hypophosphataemia               | 13 (5.8%)                      | 14 (6.3%)                             | 1 (1.3%)                                    | 0.92 (0.44, 1.90)          | -1% (-5%, 4%)         |
| Fatigue                         | 21 (9.4%)                      | 9 (4.1%)                              | 6 (7.9%)                                    | <b>2.30 (1.08, 4.91)</b>   | <b>5% (1%, 10%)</b>   |
| <b>IFM 2005-02 (March 2015)</b> |                                |                                       |   |                            |                       |
| Haematological                  |                                |                                       |   |                            |                       |
| Neutropenia                     | 158 (53.9%)                    | 21 (7.5%)                             | -   | <b>7.19 (4.70, 11.00)</b>  | <b>49% (42%, 56%)</b> |
| Leukopenia                      | 71 (24.2%)                     | 5 (1.8%)                              | -   | <b>13.57 (5.56, 33.11)</b> | <b>24% (18%, 30%)</b> |
| Thrombocytopenia                | 38 (13.0%)                     | 8 (2.9%)                              | -   | <b>4.54 (2.16, 9.56)</b>   | <b>13% (7%, 19%)</b>  |
| Non-haematological              |                                |                                       |   |                            |                       |
| Bronchitis                      | 139 (47.4%)                    | 104 (37.1%)                           | -   | <b>1.28 (1.05, 1.55)</b>   | <b>10% (2%, 18%)</b>  |
| Diarrhoea                       | 114 (38.9%)                    | 34 (12.1%)                            | -   | <b>3.20 (2.27, 4.53)</b>   | <b>27% (20%, 34%)</b> |
| Fatigue                         | 31 (10.6%)                     | 15 (5.4%)                             | -   | <b>1.97 (1.09, 3.58)</b>   | <b>5% (1%, 10%)</b>   |
| Nausea                          | 31 (10.6%)                     | 28 (10%)                              | -   | 1.06 (0.65, 1.72)          | 1% (-4%, 6%)          |
| Lung disorder                   | 19 (6.5%)                      | 3 (1.1%)                              | -   | <b>6.05 (1.81, 20.23)</b>  | <b>8% (4%, 12%)</b>   |

Abbreviations: BSC=best supportive care; CI=confidence interval; LEN=lenalidomide; XO=cross-over

Source: Table 2.5.8, p.93-94 and Table 2.5.11, p.96-97 of the submission.

Note: RR is calculated for events in the PBO group up to the point of cross-over to PBO. Statistically significant differences bolded.

**Table 17: Secondary primary malignancies with maintenance therapy across the trials**

|                 | CALGB                   |                          | RR                         | IFM 2005-02               |                         | RR                       |                          |
|-----------------|-------------------------|--------------------------|----------------------------|---------------------------|-------------------------|--------------------------|--------------------------|
|                 | LEN N=224               | BSC N=221                |                            | LEN N=306                 | BSC N=302               |                          |                          |
| <b>Mar 2015</b> |                         |                          |                            |                           |                         |                          |                          |
| SPM             | 42 <sup>b</sup> (18.8%) | 24 <sup>b</sup> (10.9%)  | <b>1.73 (1.08, 2.75)</b>   | 49 <sup>d</sup> (16%)     | 27 <sup>d</sup> (9%)    | <b>1.79 (1.15, 2.79)</b> |                          |
| Haematological  | 15 (6.7%)               | 8 (3.6%)                 | 1.85 (0.80, 4.28)          | 21 (6.9%)                 | 9 (3%)                  | <b>2.30 (1.07, 4.95)</b> |                          |
| Solid tumour    | 17 <sup>c</sup> (7.6%)  | 10 <sup>c</sup> (4.5%)   | 1.68 (0.79, 3.58)          | 21 (6.9%)                 | 13 (4.3%)               | 1.59 (0.81, 3.13)        |                          |
| Non-invasive    | 12 (5.4%)               | 9 (4.1%)                 | 1.32 (0.57, 3.06)          | 10 (3.3%)                 | 7 (2.3%)                | 1.41 (0.54, 3.66)        |                          |
| <b>Oct 2016</b> | <b>LEN N=224</b>        | <b>BSC (to XO) N=143</b> | <b>BSC (after XO) N=86</b> |                           | <b>LEN N=306</b>        | <b>BSC N=302</b>         |                          |
| SPM             | NR                      | NR                       | NR                         | -                         | 51 <sup>b</sup> (16.7%) | 33 <sup>b</sup> (10.9%)  | <b>1.53 (1.01, 2.29)</b> |
| Haematological  | 18 (7.8%)               | 3 (2.1%)                 | 0                          | <b>3.83 (1.15, 12.77)</b> | 21 <sup>c</sup> (6.9%)  | 9 (3%)                   | <b>2.30 (1.07, 4.95)</b> |
| Solid tumour    | 14 (6.1%)               | 5 (3.5%)                 | 4 (4.7%)                   | 1.79 (0.66, 4.86)         | 23 (7.5%)               | 19 (6.3%)                | 1.19 (0.66, 2.15)        |
| Non-invasive    | 11 (4.8%)               | 5 (3.5%)                 | 1 (1.2%)                   | 1.40 (0.50, 3.96)         | 10 (3.3%)               | 7 (2.3%)                 | 1.41 (0.54, 3.66)        |

Abbreviations: ASCT=autologous stem cell transplant; BSC=best supportive care; LEN=lenalidomide; NR=not reported; SPM=second primary malignancy; THAL=thalidomide; XO=crossover.

Note: a. RR calculated during the evaluation for events in the PBO group up to the point of cross-over to PBO. b Subjects with more than one type of SPM are counted once in the total. c One subject had two solid tumours and is counted once in the table. d 49 subjects randomised to lenalidomide experienced 68 SPMs and 27 subjects randomised to placebo experienced 37 SPMs. Statistically significant differences bolded.

Source: Table 2.5.15, p.106 of the submission.

- 6.29 Relative to BSC, the relevant safety outcomes for patients taking lenalidomide were SPMs and haematological AEs (neutropenia and leukopenia). In comparison, relative to BSC, the relevant safety outcome for patients taking thalidomide was peripheral neuropathy (nervous system disorders). This resulted in the submission concluding that lenalidomide and thalidomide have different safety profiles, albeit complicated by the indirect nature of the comparison.

## Benefits/harms

- 6.30 A summary of the comparative benefits and harms for lenalidomide compared to BSC is presented in the table below.

**Table 18: Summary of comparative benefits and harms for lenalidomide and BSC**

| <b>Benefits</b>                     |                     |                    |                            |                                 |            |                          |
|-------------------------------------|---------------------|--------------------|----------------------------|---------------------------------|------------|--------------------------|
|                                     | <b>Lenalidomide</b> | <b>BSC</b>         | <b>Absolute Difference</b> | <b>HR (95% CI)</b>              |            |                          |
| <b>PFS: CALGB</b>                   |                     |                    |                            |                                 |            |                          |
| Progressed <sup>a</sup> n/N (%)     | 146/231 (63.2)      | 176/229 (76.9)     | 14                         | <b>0.57 (0.46, 0.71)</b>        |            |                          |
| Median (mths)                       | 57.3 (44.2, 73.3)   | 28.9 (23.0, 36.3)  | 28.4                       | -                               |            |                          |
| Progressed <sup>b</sup> n/N (%)     | 126/231 (54.5)      | 162/229 (70.7)     | 16                         | <b>0.58 (0.46, 0.73)</b>        |            |                          |
| Median (mths)                       | 58.4 (42.7, 82.0)   | 28.9 (21.0, 35.4)  | 29.5                       | -                               |            |                          |
| <b>OS: CALGB</b>                    |                     |                    |                            |                                 |            |                          |
| Dead <sup>a</sup> n/N (%)           | 88/231 (38.1)       | 120/229 (52.4)     | 14                         | <b>0.61 (0.46, 0.80)</b>        |            |                          |
| Median (mths)                       | 113.8 (100.4, NE)   | 84.1 (73.8, 106.0) | 29.7                       | -                               |            |                          |
| Dead <sup>b</sup> n/N (%)           | 72/231 (31.2)       | 109/229 (47.6)     | 16                         | <b>0.57 (0.42, 0.76)</b>        |            |                          |
| Median (mths)                       | NR (NE, NE)         | 79.0 (70.2, 88.4)  | NE                         | -                               |            |                          |
| <b>Harms</b>                        |                     |                    |                            |                                 |            |                          |
|                                     | <b>LEN</b>          | <b>BSC</b>         | <b>RR (95% CI)</b>         | <b>Event rate/100 patients*</b> |            | <b>RD (95% CI)</b>       |
|                                     |                     |                    |                            | <b>LEN</b>                      | <b>BSC</b> |                          |
| <b>Neutropenia (Grade 3 or 4)</b>   |                     |                    |                            |                                 |            |                          |
| CALGB                               | 133/224             | 73/221             | 1.80 (1.45, 2.23)          | 59.4                            | 33.0       | <b>0.26 (0.17, 0.35)</b> |
| <b>Leukopenia (Grade 3 or 4)</b>    |                     |                    |                            |                                 |            |                          |
| CALGB                               | 45/224              | 22/221             | 2.02 (1.26, 3.24)          | 20.1                            | 10.0       | <b>0.10 (0.04, 0.17)</b> |
| <b>Secondary primary malignancy</b> |                     |                    |                            |                                 |            |                          |
| CALGB                               | 42/224              | 24/221             | 1.73 (1.08, 2.75)          | 18.8                            | 10.9       | <b>0.08 (0.01, 0.14)</b> |

Note: a Median duration of follow-up: CALGB= October 2016 data-cut is 91 months; b Median duration of follow-up: CALGB = March 2015 data cut is 72.4 months.

Abbreviations: BSC, best supportive care; HR = hazard ratio; LEN=lenalidomide; NE=not evaluable; NR= not reported; RD = risk difference; RR = risk ratio

Source: Table 2.5.1, p.80 and Table 2.5.3, p.85-86 of the submission. Absolute difference in % with events calculated during the evaluation.

6.31 On the basis of direct evidence presented in the pivotal CALGB trial, for every 100 patients treated with lenalidomide in comparison to BSC and over a median duration of follow-up 72.4 months:

- Approximately 16 more patients remained progression-free.
- Approximately 16 more patients remained alive.
- Approximately 26 more patients would have a Grade 3 or 4 neutropenic event.
- Approximately 10 more patients would have a Grade 3 or 4 leukopenic event.
- Approximately 8 more patients would have a secondary primary malignancy.

6.32 The PBAC noted the benefits summarised above were based on only one of the lenalidomide trials and the pooled efficacy results for the four lenalidomide versus BSC trials were less favourable.

6.33 A summary of the comparative benefits and harms for lenalidomide compared to thalidomide is presented in Table 19. The submission's comparison between lenalidomide and thalidomide was based on an indirect comparison of PFS and OS using CALBG results adjusted for cross-over compared to Myeloma IX. The indirect comparison between lenalidomide and thalidomide incorporating MM6 was conducted during the evaluation. The submission did not report an indirect comparison of safety outcomes. Within trial event rates were reported for nervous system disorders/peripheral neuropathy and secondary primary malignancy.

Neutropenia rates were not reported in either of the thalidomide trials, Myeloma IX or MM6.

**Table 19 Indirect comparison summary of comparative benefits and harms for lenalidomide and thalidomide**

| <b>Benefits</b>   |                                  |                                |                                |                                       |            |                                 |
|---|----------------------------------|--------------------------------|--------------------------------|---------------------------------------|------------|---------------------------------|
|   | <b>Lenalidomide</b>              | <b>BSC</b>                     | <b>Absolute Difference</b>     | <b>HR (95% CI)</b>                    |            |                                 |
| <b>PFS: CALGB (adj)</b>   |                                  |                                |                                |                                       |            |                                 |
| Progressed* n/N (%)   | NR                               | NR                             | NE <sup>§</sup>                | <b>0.52 (0.39, 0.69)</b>              |            |                                 |
| Median (mths)   | 56.9 (22.1, NE)                  | 25.8 (10.9, 66.1)              | 31.1 <sup>§</sup>              | -                                     |            |                                 |
|   | <b>Thalidomide</b>               | <b>BSC</b>                     | <b>Absolute Difference</b>     | <b>HR (95% CI)</b>                    |            |                                 |
| <b>PFS: Myeloma IX</b>  |                                  |                                |                                |                                       |            |                                 |
| Progressed* n/N (%)   | NR                               | NR                             | NE <sup>§</sup>                | <b>0.70 (0.56, 0.88)</b>              |            |                                 |
| Median (mths)   | 30 (NR)                          | 23 (NR)                        | 7 <sup>§</sup>                 | -                                     |            |                                 |
| <b>PFS: MM6</b>   |                                  |                                |                                |                                       |            |                                 |
| Progressed* n/N (%)   | NR                               | NR                             | NE                             | NR                                    |            |                                 |
| Median (mths)   | 32.4 (25.2, 38.4) <sup>§</sup>   | 18.0 (13.2, 21.6) <sup>§</sup> | 14.4 <sup>§</sup>              | <b>0.16 (0.04, 0.58)<sup>§</sup></b>  |            |                                 |
|   | <b>Lenalidomide</b>              | <b>BSC</b>                     | <b>Absolute Difference</b>     | <b>HR (95% CI)</b>                    |            |                                 |
| <b>OS: CALGB (adj)</b>  |                                  |                                |                                |                                       |            |                                 |
| Dead* n/N (%)   | NR                               | NR                             | -                              | -                                     |            |                                 |
| Median (mths)   | 111.0 (59.4, NE)                 | 72.2 (34.6, 110.7)             | 38.8                           | <b>0.51 (0.37, 0.74)</b>              |            |                                 |
|   | <b>Thalidomide</b>               | <b>BSC</b>                     | <b>Absolute Difference</b>     | <b>HR (95% CI)</b>                    |            |                                 |
| <b>OS: Myeloma IX</b>   |                                  |                                |                                |                                       |            |                                 |
| Dead* n/N (%)   | NR                               | NR                             | -                              | -                                     |            |                                 |
| Median (mths)   | NR                               | NR                             | NR                             | 1.29 <sup>a</sup>                     |            |                                 |
| <b>OS: MM6</b>  |                                  |                                |                                |                                       |            |                                 |
| Dead* n/N (%)   | NR                               | NR                             | NE                             | NR                                    |            |                                 |
| Median (mths)   | 102.0 (88.8, 116.4) <sup>§</sup> | 54.0 (46.8, 61.2) <sup>§</sup> | 48.0 <sup>§</sup>              | <b>0.12 (0.028, 0.56)<sup>§</sup></b> |            |                                 |
| <b>Harms</b>  |                                  |                                |                                |                                       |            |                                 |
|   | <b>LEN</b>                       | <b>BSC</b>                     | <b>RR (95% CI)</b>             | <b>Event rate/100 patients*</b>       |            | <b>RD (95% CI)</b>              |
|   |                                  |                                |                                | <b>LEN</b>                            | <b>BSC</b> |                                 |
| <b>Nervous system disorder</b>  |                                  |                                |                                |                                       |            |                                 |
| CALGB   | 7/224                            | 4/221                          | 1.73 (0.51, 5.82)              | 3.1                                   | 1.8        | 0.01 (-0.02, 0.04)              |
| <b>Secondary primary malignancy</b>   |                                  |                                |                                |                                       |            |                                 |
| CALGB   | 42/224                           | 24/221                         | 1.73 (1.08, 2.75) <sup>§</sup> | 18.8                                  | 10.9       | <b>0.08 (0.01, 0.14)</b>        |
|   | <b>THAL</b>                      | <b>BSC</b>                     | <b>RR (95% CI)</b>             | <b>Event rate/100 patients*</b>       |            | <b>RD (95% CI)</b>              |
|   |                                  |                                |                                | <b>THAL</b>                           | <b>BSC</b> |                                 |
| <b>Nervous system disorder (Myeloma IX) or Grade 3 or 4 Peripheral neuropathy (MM6)</b> |                                  |                                |                                |                                       |            |                                 |
| Myeloma IX (ASCT)   | 6/246                            | 1/247                          | 6.02 (0.73, 49.67)             | 2.4                                   | 0.4        | 0.02 (0.00, 0.04)               |
| MM6   | 10/114                           | 0/129                          | NE                             | 1.0                                   | 0.0        | <b>0.09 (0.04, 0.14)</b>        |
| <b>Secondary primary malignancy</b>   |                                  |                                |                                |                                       |            |                                 |
| Myeloma IX (ASCT + no ASCT)   | 12/410                           | 12/410                         | 1.00 (0.45, 2.20) <sup>§</sup> | 2.9                                   | 2.9        | 0.00 (-0.02, 0.02) <sup>§</sup> |
| MM6   | 10/104                           | 9/103                          | 1.10 (0.47, 2.60) <sup>§</sup> | 9.6                                   | 8.7        | 0.01 (-0.07, 0.09) <sup>§</sup> |

\* Median duration of follow-up: CALGB adjustment using the RPSFT method at the February 2016 data cut-off date using time from randomisation with median follow-up not reported. CALGB ITT using October 2016 data cut-off date with median follow-up 91 months from time of ASCT. CALGB safety from March 2015 data cut-off date of 72.4 months median follow-up. Myeloma IX = October 2009 data cut-off with 38 months median follow-up. MM6 = Spencer reported 2006 cut-off of 3 years median follow-up and Kalf reported December 2012 cut-off of 5.4 years median follow-up.

Abbreviations: HR = hazard ratio; NE, not evaluable; NR= not reported; PBO = placebo; RD = risk difference; RR = risk ratio

Note: a. Myeloma IX OS was estimated based on the proportion alive at 3 –years from the October 2009 data cut-off (thalidomide 75% vs observation 80%, p=0.26) assuming exponential distribution.

Figures in bold statistically significant. §Relative risk and risk difference not reported in submission were calculated during the evaluation. Kalfi 2014 reported MM6 median PFS and OS in years, this was converted into months.

Source: Table 2.6.5-6, p.120-121, Table 2.5.12, p.99-100 and Table 2.5.15, p.106 of the submission. MM6 from Spencer et al. (2009) and Kalfi et al. (2014).

6.34 The ESC considered that in the context of potentially reversible peripheral neuropathy experienced with thalidomide, compared to the considerable number of SPMs, which are irreversible and likely fatal, that lenalidomide may have inferior safety to thalidomide. The PBAC noted that a number of the consumer comments indicated a patient preference for lenalidomide due to the toxicities experienced with thalidomide. The PBAC also reflected that the longer duration of treatment with lenalidomide compared to thalidomide would likely contribute a greater number of AEs and therefore a claim of a different safety profile in the maintenance setting post-autologous transplant may be reasonable.

### **Clinical claim**

6.35 The submission described lenalidomide as superior in terms of effectiveness but inferior in terms of safety compared to BSC. The PBAC considered that the evidence presented in the submission supported this claim.

6.36 The submission described lenalidomide as superior in terms of effectiveness (specifically OS) and non-inferior in terms of safety compared to thalidomide. The ESC considered that this claim was not supported by the evidence presented, and the claim of superior OS did not appear clinically plausible given a difference in PFS was not demonstrated. The ESC also considered that it may be informative to include the MM6 trial in such a comparison, and that in this case a claim of non-inferior efficacy may be more appropriate.

6.37 The PBAC considered that the claim of superior comparative efficacy compared to thalidomide was not adequately supported by the data. The PBAC considered that a claim of non-inferior efficacy compared to thalidomide may be more appropriate. The PBAC considered that the claim of different safety may be reasonable.

### **Economic analysis**

6.38 The submission presented a stepped economic evaluation based on evidence from the RCTs and implemented a modelled cost-utility analysis for lenalidomide vs. BSC. The submission also presented a modelled cost-utility analysis based on the indirect comparison of lenalidomide and thalidomide.

6.39 The PBAC considered that given the claim of superior efficacy for lenalidomide compared to thalidomide was not accepted, a cost-minimisation analysis may be a more appropriate form of economic analysis by which to compare lenalidomide and thalidomide.

**Table 20: Summary of model structure and rationale**

| Component                        | Summary  |
|----------------------------------|--|
| Time horizon                     | 25 years in the model base case versus 6 years in CALGB.   |
| Outcomes                         | LYG and QALYs.   |
| Methods used to generate results | Cohort expected value, partitioned survival model.   |
| Health states                    | Six model health states, comprising: pre-progression (split into 'on treatment' and 'off treatment'); post-progression (split into 'pre-second-line treatment', 'second-line treatment' and 'post second-line treatment'); death.  |
| Cycle length                     | 28 days.   |
| Transition probabilities         | Lenalidomide vs. BSC:<br>Area under the curve analysis from the CALGB trial using cross-over adjusted OS and PFS.<br>Lenalidomide vs. thalidomide:<br>HR of lenalidomide vs. thalidomide from indirect comparison between cross-over adjusted CALGB and Myeloma IX. OS HR estimated as 0.40 and PFS indirect comparison was not statistically different, so a HR=1 was applied in the model. |

Abbreviations: BSC=best supportive care; HR=hazard ratio; LY=life-year; PFS=progression-free survival; QALY, quality adjusted life year; OS=overall survival.

Source: Table 3.1.1, p.144 of the submission.

6.40 Both models applied fitted survival curves for the entire time horizon. The ESC considered that this was inappropriate as Kaplan-Meier data should have been applied for the period for which they were available and reliable, at least up to the median duration of follow-up, with extrapolations applied thereafter. The ESC noted that the fitted curves appeared to overestimate the Kaplan-Meier data for lenalidomide, and provide a reasonable fit to those for the relevant comparator. The use of these fitted functions to inform the model over the entire time horizon thus biased the analyses in favour of lenalidomide. The PBAC considered that the approach taken by the submission was inappropriate and advised that any future submission should use the Kaplan-Meier data at least to the median duration of follow-up.

6.41 The submission applied a time horizon of 25 years with extrapolation based on the CALGB trial. This may be inappropriate given the natural history of NDMM and only 6 years median follow up in CALGB at the 1<sup>st</sup> March 2015 cut-off for surviving subjects after maintenance randomisation. The July 2015 lenalidomide submission for NDMM patients who are ineligible for ASCT used a time horizon for lenalidomide vs. thalidomide of 15 years (p.16 lenalidomide PSD November 2015). While it is possible that a longer time horizon than 15 years is appropriate for patients eligible for ASCT given they are generally healthier than those ineligible for ASCT, an additional 10 years may not be justified. The ESC noted recently published data estimate median survival of 6-7 years<sup>5</sup>, and while this may be because the full benefits of the novel therapies have not yet been observed, this indicates that there is limited justification for increasing the time horizon substantially beyond the

<sup>5</sup> Rajkumar V 2016. Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. *American Journal of Haematology*. 7:719-34

15 years previously accepted in a similar situation. The PBAC agreed with the ESC and noted that sensitivity analyses presented in the pre-PBAC response included a 15 year time-horizon. The PBAC advised that any future submission should apply a 15 year time horizon.

6.42 The submission used CALGB as the basis of the efficacy estimates for lenalidomide and BSC, and time on treatment (ToT) for lenalidomide, but IFM 2005-02 to estimate the lenalidomide dose per cycle. The dose per cycle was not available for CALGB. There is thus a mismatch between the assumed efficacy and the drug dose required to achieve it used within the economic evaluation.

6.43 The key drivers of the lenalidomide vs. BSC model are presented in Table 21.

**Table 21: Key drivers of the model – lenalidomide vs. BSC**

| Description                | Method/Value   | Impact                      |
|----------------------------|--|-----------------------------|
| Extrapolation              | Treatment effect continued beyond 6-year period for up to 25 years   | High, favoured lenalidomide |
| Extrapolation data source  | Data for OS, PFS and ToT from CALGB rather than pooled from trial dataset (CALGB, IFM 2005-02, GIMEMA)                             | High, favoured lenalidomide |
| Time on subsequent therapy | Time (cycles) on post-progression treatment based on expert opinion rather than pooled across lines of therapy and group in GIMEMA | High, favoured lenalidomide |

Abbreviations: PFS=progression-free survival; OS=overall survival; ToT=time on treatment.

Source: Table 3.9.1, p. 190 of the submission.

6.44 The key drivers of the lenalidomide vs. thalidomide model are presented in Table 22.

**Table 22: Key drivers of the model – lenalidomide vs. thalidomide**

| Description                              | Method/Value   | Impact                             |
|--|--|------------------------------------|
| Extrapolation                            | Treatment effect continued beyond 6-year period for up to 25 years   | High, favoured lenalidomide        |
| Extrapolation data source                | Data for OS, PFS and ToT from CALGB rather than pooled from trial dataset (CALGB, IFM 2005-02, GIMEMA)   | High, favoured lenalidomide        |
| Extrapolation PFS                        | Functional form for PFS in base case was generalised gamma.  | Moderate, favoured lenalidomide    |
| Extrapolation HR for OS for THAL vs. LEN | HR for thalidomide vs BSC was estimated from Myeloma IX based on 3-year OS rate in each arm. The resulting HR of 0.4 (inverse 2.52 applied in model) from the indirect comparison was applied to the fitted LEN curves for OS. The ESC considered that applying a constant hazard ratio to determine the thalidomide OS was not justified and inappropriate. | High, likely favoured lenalidomide |
| Time on subsequent therapy               | Time (cycles) on post-progression treatment based on expert opinion rather than pooled across lines of therapy and group in GIMEMA   | High, favoured lenalidomide        |

Abbreviations: PFS=progression free survival; OS=overall survival; ToT= time on treatment.

Source: Table 3.9.2, p. 191 of the submission.

6.45 The results of the stepped economic evaluation for lenalidomide vs. BSC are presented in Table 23. The extension of the time horizon to 25 years (Step 2) from 6 years (Step 1) has a significant impact on the ICER by increasing the incremental LY gained from 0.58 to 3.11. Extension of the time horizon therefore accounts for 81% of the estimated incremental LY. Including all costs in Step 3 (post-progression drug, health care resource utilisation (HCRU) and AEs in 1st, 2nd line and post-2nd line), and not just first line drug costs, increased the cost of BSC from \$ [redacted] to \$ [redacted]. The inclusion of all costs in Step 3 also increased the costs in lenalidomide but as more

patients progress on BSC, the incremental cost reduced. Applying QoL transformations in Step 4 increased the ICER to \$15,000 - \$45,000 per QALY gained.

**Table 23: Results of the stepped economic evaluation – Lenalidomide vs. BSC**

| Step and component   | Lenalidomide  | BSC           | Increment     |
|--|---------------|---------------|---------------|
| <b>Step 1: CALGB extrapolation (cross-over adjusted, median follow-up 6 years) – 1<sup>st</sup> line drug costs and outcomes</b> |               |               |               |
| Costs  | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYG  | 4.71          | 4.13          | 0.58          |
| Incremental cost per LYG gained  |               |               |               |
| <b>Step 2: time horizon extended to 25 years</b>   |               |               |               |
| Costs  | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYG  | 8.50          | 5.39          | 3.11          |
| Incremental cost per LYG gained  |               |               |               |
| <b>Step 3: incorporation of all costs (subsequent therapy, AEs)</b>  |               |               |               |
| Costs  | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYG  | 8.50          | 5.39          | 3.11          |
| Incremental cost per LYG gained  |               |               |               |
| <b>Step 4: utility weights applied</b>   |               |               |               |
| Costs  | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALYs  | 6.52          | 4.08          | 2.44          |
| <b>Incremental cost per QALY gained (base case)</b>  |               |               |               |
| \$ [REDACTED]  |               |               |               |

Abbreviations: AE = adverse events.

Source: Table 3.8.1, p.184 of the submission. Excel spreadsheet 'Att 12\_Section 3 cost effectiveness model v2'\_ sheet "Results" so that LYG and QALYs are reported to 2 decimal places.

6.46 The results of the stepped economic evaluation for lenalidomide vs. thalidomide are presented in Table 24. The extension of the time horizon accounts for 77% of the estimated incremental LY. The remaining impacts of the additional steps are as described for the comparison of lenalidomide with BSC, with Step 4 culminating in a cost per QALY gained of \$45,000 - \$75,000.

**Table 24: Results of the stepped economic evaluation – lenalidomide vs. thalidomide**

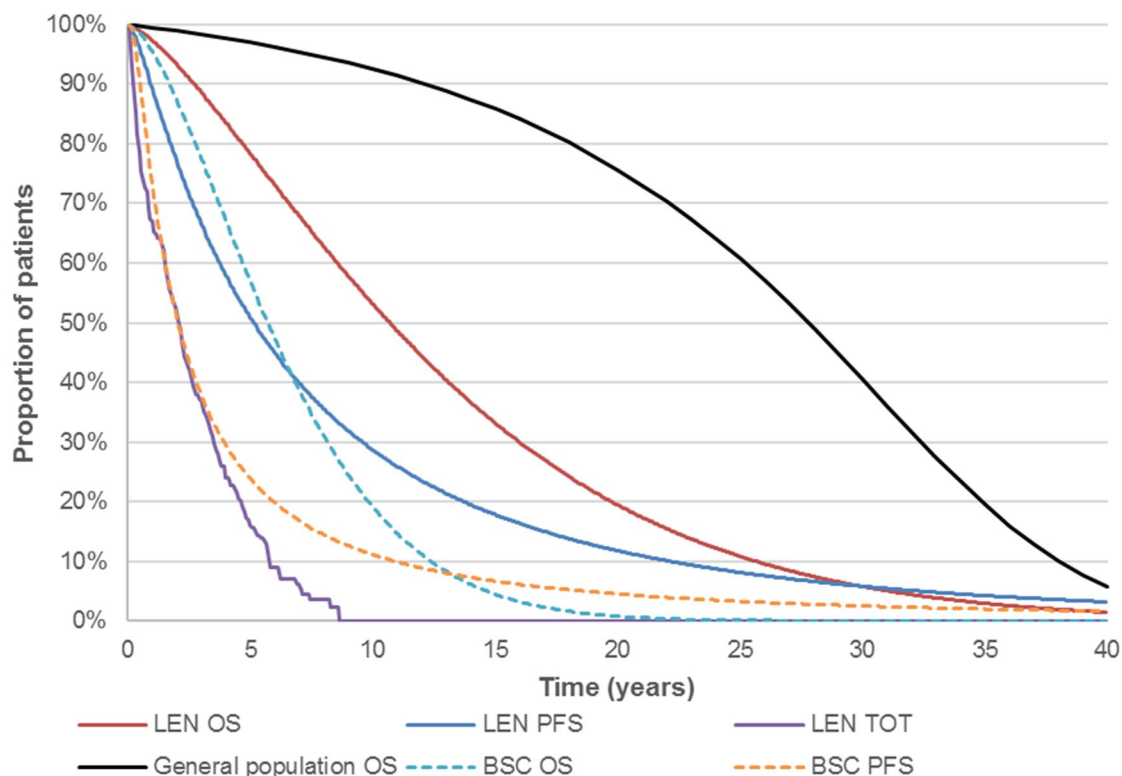
| Step and component   | Lenalidomide  | Thalidomide   | Increment     |
|--|---------------|---------------|---------------|
| <b>Step 1: CALGB extrapolation (cross-over adjusted) -based costs and outcomes</b> |               |               |               |
| Costs  | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYG  | 4.71          | 3.99          | 0.72          |
| Incremental cost per LYG gained  |               |               |               |
| <b>Step 2: time horizon extended to 25 years</b>                                   |               |               |               |
| Costs  | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYG  | 8.50          | 5.32          | 3.18          |
| Incremental cost per LYG gained  |               |               |               |
| <b>Step 3: incorporation of all costs (subsequent therapy, AEs.)</b>               |               |               |               |
| Costs  | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYG  | 8.50          | 5.32          | 3.18          |
| Incremental cost per LYG gained  |               |               |               |
| <b>Step 4: utility weights applied</b>   |               |               |               |
| Costs  | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALYs  | 6.52          | 4.13          | 2.39          |
| <b>Incremental cost per QALY gained (base case)</b>                                |               |               |               |
| \$ [REDACTED]  |               |               |               |

Abbreviations: AE = adverse events

Source: Table 3.8.1, p.184 of the submission. Excel spreadsheet 'Att 12\_Section 3 cost effectiveness model v2'\_ sheet "Results" so that LYG and QALYs are reported to 2 decimal places.

- 6.47 The ESC noted that the inverse HR for OS from the indirect comparison was applied to the lenalidomide fitted survival curve to estimate the OS for thalidomide. The ESC noted that the HR had been estimated based on data at a single point in time (OS at 3 years). The ESC considered that the resulting HR was unreliable, and further applying a constant HR for the model duration was unjustified. A comparison of the results for the lenalidomide vs BSC and lenalidomide vs thalidomide models further indicated that the approach may not be valid, and that results were implausible, with patients in the thalidomide arm having worse overall survival than the BSC arm (thalidomide LYG 5.32; BSC LYG 5.39). The PBAC considered, notwithstanding that superior OS had not been established for lenalidomide compared to thalidomide, that the economic model was unreliable and insufficiently justified, and based on thalidomide data from the Myeloma IX trial which were less favourable than for the other thalidomide maintenance trials.
- 6.48 The submission noted that there was no crossing of OS, PFS and ToT curves for most of the projections (Figure 5). However, in the model the fitted PFS curves exceeded OS after 30 years for lenalidomide and after 12 years for BSC. Moreover, there was convergence (post year-35) of PFS for BSC and OS for lenalidomide. The pre-PBAC response (p2) stated that a correction was applied in the model by calculating the transition probability for progression as the inverse of the ratio of the proportions of patients who are progression-free in the current vs previous cycle (from the fitted PFS curve), less the transition probability for death, and set to zero when this is negative. However, the PBAC considered that this may not have sufficiently addressed the issue that the chosen curves generated an implausible profile of disease progression, and that the impact of selecting curves such that PFS and OS did not cross, rather than applying an adjustment, was unknown and therefore this introduced uncertainty into the model.

Figure 5: Comparison of long-term survival projections, lenalidomide and best supportive care



Source: Figure 3.7.1, p.182 of the submission. Source: Figure 3.7.2, p.183 of the submission. Plotted on the same chart during the evaluation using 'Att 12\_Section 3 cost effectiveness model v2'.

6.49 The univariate sensitivity analyses resulting in variations of more than 5% for the model comparing lenalidomide with BSC are presented in Table 25. These results show that the model was most sensitive to variations in the time horizon, the source of efficacy data and the time patients spend on subsequent treatment post-progression.

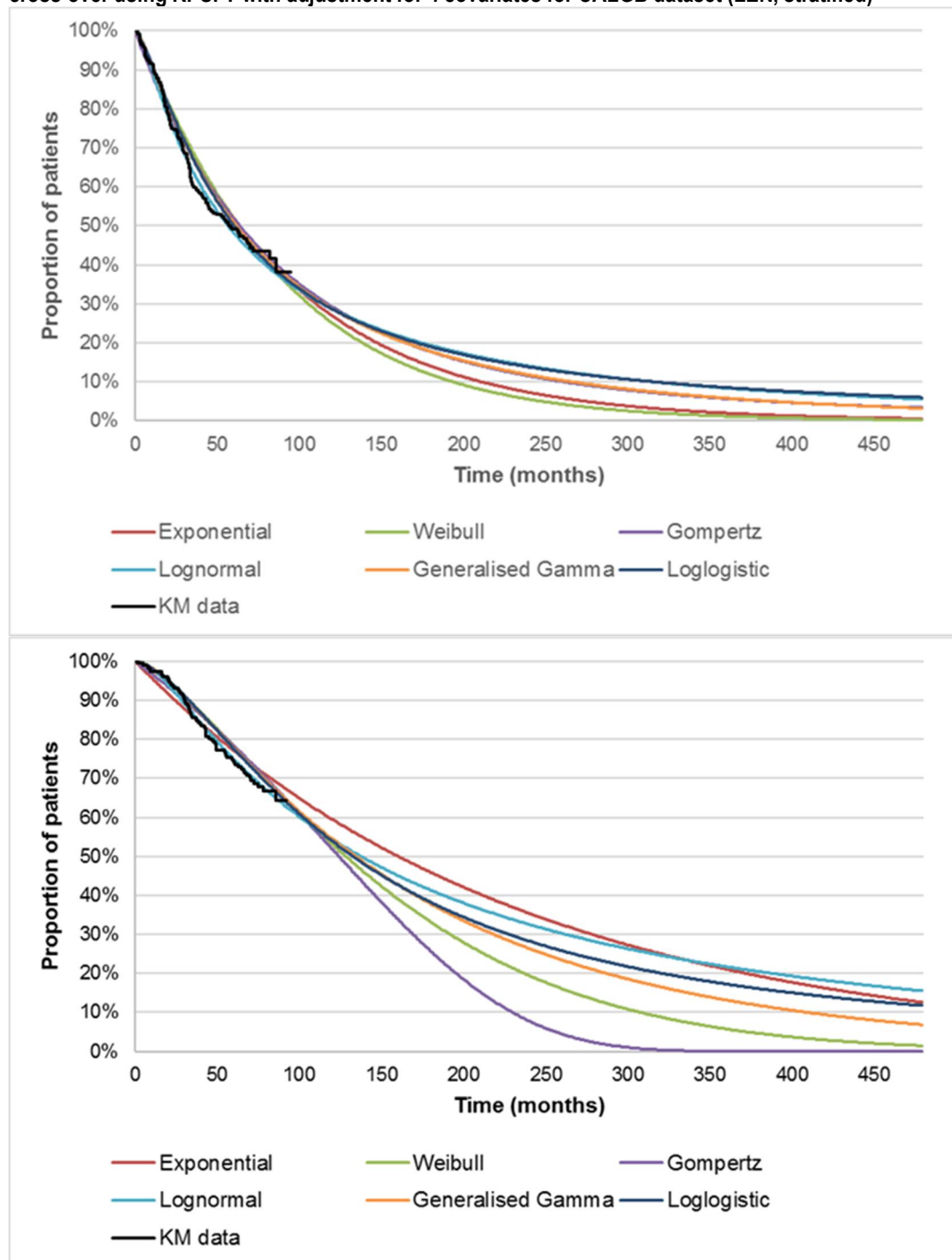
**Table 25: Results of sensitivity analyses – lenalidomide vs. BSC**

| Analyses   | Incremental cost | Incremental QALY | ICER          |
|--|------------------|------------------|---------------|
| <b>Base case</b>   | \$ [REDACTED]    | 2.44             | \$ [REDACTED] |
| Discount rate (base case 5% costs and outcomes)  |                  |                  |               |
| 0% costs and outcomes  | \$ [REDACTED]    | 4.22             | \$ [REDACTED] |
| 3.5% costs and outcomes  | \$ [REDACTED]    | 2.85             | \$ [REDACTED] |
| Time horizon (base case 25 years)  |                  |                  |               |
| 6 years  | \$ [REDACTED]    | 0.51             | \$ [REDACTED] |
| 10 years   | \$ [REDACTED]    | 1.17             | \$ [REDACTED] |
| 15 years   | \$ [REDACTED]    | 1.85             | \$ [REDACTED] |
| 20 years   | \$ [REDACTED]    | 2.25             | \$ [REDACTED] |
| PFS extrapolation (base case Generalised Gamma extrapolation)                                      |                  |                  |               |
| Log-Logistic extrapolation   | \$ [REDACTED]    | 2.44             | \$ [REDACTED] |
| Weibull extrapolation  | \$ [REDACTED]    | 2.43             | \$ [REDACTED] |
| OS, PFS and ToT extrapolation source (base case CALGB source)                                      | \$ [REDACTED]    | 1.03             | \$ [REDACTED] |
| Pooled trial dataset (CALGB, IFM 2005-02 and GIMEMA)   |                  |                  |               |
| Utility with progressed disease 3rd line treatment (base case 0.725 – panobinostat NICE Appraisal) | \$ [REDACTED]    | 2.85             | \$ [REDACTED] |
| 0.738 (progressed disease 2nd line treatment - CONNECT)  |                  |                  |               |
| Time on subsequent treatment (expert opinion, GIMEMA)  |                  |                  |               |
| Pooled data (lines/groups) GIMEMA  | \$ [REDACTED]    | 2.44             | \$ [REDACTED] |

Source: Table 3.9.1, p. 190 of the submission. Excel spreadsheet 'Att 12\_Section 3 cost effectiveness model v2'\_ sheet 'Results'.

6.50 The fitted PFS and OS curves for lenalidomide are presented in Figure 6. The PBAC noted that this showed that none of the extrapolated curves appear to fit the Kaplan-Meier data well for the lenalidomide arm, overestimating PFS and OS. The corresponding figures for BSC suggest that the fitted curves were a reasonable approximation for the Kaplan-Meier data for BSC (both PFS and OS). The result is that the fitted curves appear to overestimate the gain for lenalidomide over BSC for the Kaplan-Meier period.

Figure 6: Fit of the extrapolated survival curves to the KM data for PFS (top) and OS (bottom) with adjustment for cross-over using RPSFT with adjustment for 4 covariates for CALGB dataset (LEN, stratified)



Source: Figure 3.4.2 and 3.4.3, p.162-163 of the submission.

6.51 The ESC noted that when extrapolating to 25 years, 81% of the LY gain was from the extrapolation period, and therefore that the incremental benefit of lenalidomide was dependent on both the time horizon and extrapolation method. The submission

argued that the “best statistical fit to the RPSFT crossover adjusted dataset (4 covariate analysis) are Weibull or log-logistic” and that Weibull was chosen on the basis of “better statistical fit, better visual fit” and “the only curve to give clinically plausible results”. The PBAC agreed with the ESC’s questioning of whether the Weibull could reasonably be considered clinically plausible given that the OS and PFS curves cross, and noted that an additional multivariate sensitivity analysis showed that applying the log-logistic extrapolation function to OS with a 15 year time horizon increased the ICER/QALY to \$45,000 - \$75,000, compared to \$15,000/QALY - \$45,000/QALY when applying the Weibull curve as used in the submission with a 15 year time horizon.

**Table 26. Sensitivity analysis of extrapolation functions applied to OS for 15 year time horizon**

| Lenalidomide vs. BSC (15 year time horizon) | Incremental cost | Incremental QALY | ICER          |
|---|------------------|------------------|---------------|
| One-way sensitivity analysis                |                  |                  |               |
| OS – Weibull                                | \$ [REDACTED]    | 1.85             | \$ [REDACTED] |
| Multivariate sensitivity analysis           |                  |                  |               |
| OS - exponential                            | \$ [REDACTED]    | 1.70             | \$ [REDACTED] |
| OS - Gompertz                               | \$ [REDACTED]    | 1.95             | \$ [REDACTED] |
| OS - log normal                             | \$ [REDACTED]    | 1.70             | \$ [REDACTED] |
| OS - generalised gamma                      | \$ [REDACTED]    | 1.93             | \$ [REDACTED] |
| OS - log logistic                           | \$ [REDACTED]    | 1.66             | \$ [REDACTED] |

6.52 The ESC noted that the economic analysis comparing lenalidomide with thalidomide indicated that the model was most sensitive to variations in the HR for OS and PFS for lenalidomide compared to thalidomide and the time horizon (ICER/QALY \$45,000/QALY - \$75,000/QALY for 15 year time horizon), and noted the issues raised with both of these factors.

6.53 The ESC noted the cost-effectiveness ratios presented in the PSCR based on a modelled time horizon of 15 years and weighted based on the expected replacement of BSC and thalidomide. The ESC did not consider these results informative given the issues noted with the thalidomide model and derivation of the weights.

**Table 27: Results of sensitivity analyses – lenalidomide vs. thalidomide**

| Analyses   | Incremental cost | Incremental QALY | ICER          |
|--|------------------|------------------|---------------|
| <b>Base case</b>   | \$ [REDACTED]    | 2.39             | \$ [REDACTED] |
| Discount rate (base case 5% costs and outcomes)  |                  |                  |               |
| 0% costs and outcomes  | \$ [REDACTED]    | 4.10             | \$ [REDACTED] |
| 3.5% costs and outcomes  | \$ [REDACTED]    | 2.78             | \$ [REDACTED] |
| Time horizon (base case 25 years)  |                  |                  |               |
| 6 years  | \$ [REDACTED]    | 0.56             | \$ [REDACTED] |
| 10 years   | \$ [REDACTED]    | 1.20             | \$ [REDACTED] |
| 15 years   | \$ [REDACTED]    | 1.84             | \$ [REDACTED] |
| 20 years   | \$ [REDACTED]    | 2.21             | \$ [REDACTED] |
| PFS extrapolation (base case Generalised Gamma)  |                  |                  |               |
| Log-Logistic extrapolation   | \$ [REDACTED]    | 2.39             | \$ [REDACTED] |
| Weibull extrapolation  | \$ [REDACTED]    | 2.37             | \$ [REDACTED] |
| OS, PFS and ToT extrapolation source (base case CALGB)   |                  |                  |               |
| Pooled trial dataset (CALGB, IFM 2005-02 and GIMEMA)   | \$ [REDACTED]    | 2.15             | \$ [REDACTED] |
| Adverse event source (base case CALGB)   |                  |                  |               |
| Pooled trial dataset   | \$ [REDACTED]    | 2.39             | \$ [REDACTED] |
| Utility with progressed disease 3rd line treatment (base case 0.725 – panobinostat NICE Appraisal) |                  |                  |               |
| 0.738 (progressed disease 2nd line treatment - CONNECT)  | \$ [REDACTED]    | 2.42             | \$ [REDACTED] |
| Inverse HR for OS for THAL vs. LEN (base case 2.52)  |                  |                  |               |
| 1.52 (lower 95% CI limit)  | \$ [REDACTED]    | 1.14             | \$ [REDACTED] |
| 4.21 (lower 95% CI limit)  | \$ [REDACTED]    | 3.47             | \$ [REDACTED] |
| HR for PFS for THAL vs. LEN (base case 1.00)   |                  |                  |               |
| 1.34 (point estimate)  | \$ [REDACTED]    | 2.42             | \$ [REDACTED] |

Source: Table 3.9.2, p. 191 of the submission. Compiled during the evaluation using Excel spreadsheet 'Att 12\_Section 3 cost effectiveness model v2'\_ sheet 'Results'.

6.54 In addition to the issues identified above, the PBAC also noted the following issues that should be addressed in any future submission:

- Different sources were used for deriving the time on treatment, dosing, and effectiveness of lenalidomide which were not sufficiently justified or adjusted for.
- The time on treatment in the lenalidomide vs thalidomide model was assumed to be the same between the two arms, which resulted in patients being assumed to remain on thalidomide treatment (and thus incurring costs) for longer than in the trials, without any additional efficacy. This is unreasonable and biases the analysis of cost-effectiveness in favour of lenalidomide.
- The utility values in the pre-progression state in the lenalidomide vs BSC model were higher for patients on lenalidomide treatment compared to those on BSC. This is inconsistent with the data presented, and the submission's clinical claim that lenalidomide has inferior safety compared to BSC.
- The diagnostic and investigational costs applied were not well justified.
- Thalidomide was excluded as a potential post-progression treatment in the lenalidomide vs BSC model.
- There were separate states for pre-progression on treatment and pre-progression off treatment. A large proportion of the QALY gain in the pre-progression state came from the 'pre-progression, off-treatment' phase, approximately 2/3 for the lenalidomide vs BSC model. Further, the duration of lenalidomide treatment is estimated as 2.5 years, which is substantially less than the 4.579 QALYs in the pre-progression state for the lenalidomide arm. This is inconsistent with the submission's proposal that lenalidomide treatment should continue until disease progression, and attributes a greater survival benefit without incurring additional costs.

### **Drug cost/patient/year**

6.55 The average cost of lenalidomide per patient per 28-day cycle was estimated to be \$ [REDACTED] based on the proposed effective pack prices and the dose distribution in the IFM 2005-02 trials. The resulting average dispensed cost of lenalidomide per patient per year was \$ [REDACTED] ( $\$ [REDACTED] \times 365.25/28$ ).

6.56 The dispensed price of thalidomide is \$ [REDACTED] per 100 mg capsule (DPMQ of \$ [REDACTED] divided by maximum quantity of 112). The average cost of thalidomide per patient per 28-day cycle is \$ [REDACTED] ( $\$ [REDACTED]$  per capsule for 28 capsules) and the total cost per year is \$ [REDACTED] ( $\$ [REDACTED] \times 365.25/28$ ).

6.57 The duration of treatment for lenalidomide and thalidomide in the maintenance setting is different. In the financial estimates, the submission applied the treatment duration (average years) as observed in the clinical studies to estimate drug costs. The treatment duration applied in the financial estimates for lenalidomide and

thalidomide was 2.5 years and 0.6 years (7/12 months), respectively. The difference for treatment duration for thalidomide of 2.5 years applied in the economic evaluation compared with 7 months applied in the financial estimates resulted in a substantial difference in the average drug cost per treated patient in those two analyses.

**Table 28: Cost of drug treatment in the economic model and financial estimates**

|              | Average cost per patient per year | Average drug cost in economic model (Undiscounted) | Average drug cost in economic model (Discounted) | Average drug cost in financial estimates per treatment course |
|--------------|-----------------------------------|--|--|---|
| Lenalidomide | \$ [REDACTED]                     | \$ [REDACTED]                                      | \$ [REDACTED]                                    | \$ [REDACTED]   |
| Thalidomide  | \$ [REDACTED]                     | \$ [REDACTED]                                      | \$ [REDACTED]                                    | \$ [REDACTED]   |

Note: a. Lenalidomide = \$ [REDACTED] \* (365.25/28). b. Thalidomide = \$ [REDACTED] \* (365.25/28). c. Total PBS/RPBS cost divided total patients: \$ [REDACTED] per patient per year \* 2.5 years median duration of treatment. d. Total PBS/RPBS cost divided by total patients = \$ [REDACTED] per patient per year \* 0.7 years median duration of treatment.

Thalidomide = total PBS/RPBS cost divided total patients for 0.6 years median duration of treatment.

Source: Excel spreadsheet "Att 12\_Section 3 cost effectiveness model v2", sheet 'Calc Tx1' and 'Calc Tx2'.

Excel spreadsheet "Att 14\_Section 4 financial impact model v2", sheet '4.2 Proposed medicine' and '4.3 Other medicines'.

### Estimated PBS usage & financial implications

6.58 This submission was considered by DUSC. The submission presented an epidemiological approach which assumed that lenalidomide uptake would be for all patients who have received an ASCT. The submission based the number of patients receiving an ASCT on published estimates of patients undergoing an ASCT for NDMM. These estimates were based on the number of ASCT patient reported in the Australasian Bone Marrow Transplant Recipient Registry Annual Data Summary in 2013 ([REDACTED]) and 2015 ([REDACTED]), to which a [REDACTED]% annual growth rate was applied to estimate [REDACTED] patients in Year 1 (2018). DUSC noted that limited demographic and transplant data is captured in the registry on patients who choose not to give consent to transfer their information to the registry. DUSC considered that while this suggests that the ABMTRR is population-based as it collects some limited information for non-consenting patients, it is unknown what proportion of the overall multiple myeloma population were represented in the ABMTRR. DUSC agreed with the Commentary that it was also unclear what proportion of patients receiving an ASCT was newly diagnosed.

6.59 The estimated use and financial implications of lenalidomide are presented in Table 24.

**Table 24: Estimated use and financial implications**

|   | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|--------|--------|--------|--------|--------|--------|
| <b>Estimated extent of use</b>  |        |        |        |        |        |        |
| Number of ASCT  | █      | █      | █      | █      | █      | █      |
| Patients starting LEN in year <sup>a</sup>  | █      | █      | █      | █      | █      | █      |
| Patients continuing LEN from previous year <sup>b</sup>   |        | █      | █      | █      | █      | █      |
| Number of patients treated  | █      | █      | █      | █      | █      | █      |
| Number of packs dispensed <sup>c</sup>  | █      | █      | █      | █      | █      | █      |
| <b>Estimated financial implications of lenalidomide</b>   |        |        |        |        |        |        |
| Cost to PBS/RPBS  | \$ █   | \$ █   | \$ █   | \$ █   | \$ █   | \$ █   |
| Copayments  | \$ █   | \$ █   | \$ █   | \$ █   | \$ █   | \$ █   |
| Cost to PBS/RPBS less copayments  | \$ █   | \$ █   | \$ █   | \$ █   | \$ █   | \$ █   |
| <b>Estimated financial implications for thalidomide (cost savings from substituted thalidomide)</b> |        |        |        |        |        |        |
| Cost to PBS/RPBS  | -\$ █  | -\$ █  | -\$ █  | -\$ █  | -\$ █  | -\$ █  |
| Copayments  | -\$ █  | -\$ █  | -\$ █  | -\$ █  | -\$ █  | -\$ █  |
| Cost to PBS/RPBS less copayments  | -\$ █  | -\$ █  | -\$ █  | -\$ █  | -\$ █  | -\$ █  |
| <b>Net financial implications</b>   |        |        |        |        |        |        |
| Net cost to PBS/RPBS  | \$ █   | \$ █   | \$ █   | \$ █   | \$ █   | \$ █   |

Note: a Based on the sponsor's assumptions for lenalidomide uptake of █% in Year 1 increasing to █% in Year 6.

b. Continuing patients in a given year are calculated as the sum of initiators over the previous two years. e.g. █ in Year 4 = █ in Year 2 + █ in Year 3.

c. Assuming 13.04 (365.25/28) per year as estimated by the submission.

There was a minor discrepancy between the patient numbers reported in the submission and the attached Excel spreadsheet. Numbers shown are from the spreadsheet (as per Source).

Source: Table 4.9, p.200 of the submission. Excel spreadsheet 'Att14\_Section 4 financial impact model v2', sheet "4.2 Proposed medicine", sheet "4.3 Other medicines".

6.60 The PBAC noted that the DUSC considered that the financial estimates presented in the submission are uncertain with the main issues being:

- The existing pool of patients that may receive maintenance therapy with lenalidomide in the first year of listing have not been factored into the estimates. This would include patients currently on thalidomide who may switch to lenalidomide and patients who have discontinued maintenance thalidomide due to toxicity but have not yet experienced their first post-ASCT disease progression.
- However, the treated population and number of prescriptions are likely to have been overestimated as:
  - The number of patients is based on the number of transplants from the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR). It is unknown what proportion of the overall multiple myeloma population were represented in the ABMTRR. Further, the number, and definition, of newly diagnosed multiple myeloma patients represented in this registry is unknown.

- It is expected that some patients will have transplant failures and not proceed to maintenance therapy.
- The estimated number of patients receiving ASCT in Year 1 (■) is uncertain and likely overestimated.
  - The predicted number of ASCTs was extrapolated from the number of ASCTs in the ABMTRR in 2013 (■) and 2015 (■) and annual growth in this period (■%). DUSC considered the rate of increase to be unreliable as it is based on only two estimates, and is high relative to the growth in the general population.
  - DUSC noted that triangulation of the predicted number of ASCTs with PBS data for the number of patients receiving PBS subsidised bortezomib for induction therapy (n=459 in 2017) indicates a potential overestimate in the submission estimates. The clinician survey provided by the sponsor with the pre-subcommittee response (n=30 haematologists) suggests 97% of induction regimens include bortezomib. DUSC did however note that the clinician survey may not be a reliable source as the level of experience of the respondents in treating NDMM is unknown and potential sources of reporting bias were not addressed.
- Some patients will not receive lenalidomide due to the risk of Second Primary Malignancy. The PBAC considered that this would be rare.
- There is no adjustment to the number of prescriptions in the first year of listing to account for incident maintenance therapy patients commencing treatment throughout the year.

6.61 The PBAC also noted that the pre-PBAC response (p3) acknowledged the DUSC's concerns and provided updated financial estimates based on the concerns raised, specifically:

- The numbers of patients undergoing ASCT for NDMM are estimated from DUSC's re-analysis of bortezomib induction therapy (459 initiators in 2017) and clinical survey data reporting 97% of induction regimens include bortezomib, which suggest there were 473 (459/0.97) ASCTs performed in NDMM patients in 2017.
- The growth in ASCTs is assumed to be in line with general population growth.
- The proportions of patients receiving thalidomide or BSC in current practice of 47.0% and 53.0% as per the MRDR analysis (Bergin et al 2017).
- The proportion of patients taking up lenalidomide is ■% in each year, consistent with some patients not using lenalidomide due to the risk of SPM or other reasons.

6.62 The pre-PBAC response also acknowledged that some patients who have already had an ASCT and have not yet progressed may take up lenalidomide if it is listed on the

PBS, but did not include these patients in the revised estimates. The updated estimates resulted in a financial impact of \$10 - \$20 million in the first year of listing, increasing to \$30 - \$60 million in year 5 of listing, with a total of more than \$100 million over the first 5 years of listing.

### **Quality Use of Medicines**

- 6.63 The submission did not raise any quality use of medicines issues associated with the listing of lenalidomide in this setting. A post-marketing surveillance study was not proposed.
- 6.64 The DUSC considered that the risk of SPM should be considered before initiating on lenalidomide; the use of standard cancer screening for the occurrence of SPMs before and during treatment with lenalidomide is recommended in the draft Product Information.

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

- 6.65 The submission did not propose a risk-share arrangement. The PBAC considered that due to the very high potential financial impact of this listing, and risk of longer than expected duration of use, a risk-sharing arrangement would be appropriate.

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

## **7 PBAC Outcome**

- 7.1 The PBAC decided not to recommend the listing of lenalidomide for the maintenance treatment of patients with multiple myeloma following an Autologous Stem Cell Transplant (ASCT) on the basis that acceptable cost-effectiveness over other available therapies had not been demonstrated.
- 7.2 The PBAC acknowledged the consumer comments received indicated a preference for lenalidomide over thalidomide in the maintenance setting, particularly because of its lower rates of peripheral neuropathy, which consumers indicated had a considerable impact on quality of life.
- 7.3 The PBAC noted that thalidomide was recommended and used as maintenance treatment post-ASCT in current Australian clinical practice and considered it to be a relevant comparator. The PBAC also noted the data presented by the submission that indicated that not all patients receive thalidomide with a proportion receiving BSC (no active maintenance treatment). The PBAC considered the majority of patients who do not receive thalidomide post-ASCT are those patients unable to tolerate thalidomide due to adverse events such as neuropathy, somnolence and constipation. The PBAC considered, if listed, these patients would be treated with lenalidomide. Thus, the PBAC considered a mixed comparator of thalidomide and BSC to be reasonable, however noted the weightings that should be applied to each treatment were unclear and inadequately justified in the submission. Regarding the

weightings, the PBAC noted clinician advice indicated that the proportion of patients using thalidomide for post-ASCT maintenance may be higher than the proportion estimated by the Myeloma and Related Diseases Registry (MRDR).

#### **Lenalidomide versus BSC**

- 7.4 The PBAC noted that the submission identified four randomised trials comparing lenalidomide to placebo as maintenance treatment following ASCT (CALGB, IFM 2005-002, GIMEMA and Myeloma XI), although in two of these trials (GIMEMA and Myeloma XI) not all patients had undergone an ASCT. The PBAC considered the evidence from all four trials to be relevant, and that it may be appropriate to utilise the ITT results from the GIMEMA and Myeloma XI trials given that prior ASCT did not appear to be a treatment effect modifier with similar PFS and OS results for the subgroups with and without prior ASCT. The PBAC noted that updated data for the Myeloma XI study were presented in December 2017 and should be published in full in the near future, and considered that these data would be informative.
- 7.5 The PBAC noted that treatment with lenalidomide compared to BSC resulted in a statistically significant improvement in progression-free survival (PFS) in each of the four trials. However, a statistically significant improvement in overall survival (OS) was only observed in the CALGB trial. The PBAC acknowledged that crossover in CALGB, and unblinding in IFM 2005-002 may have diluted the treatment effect of lenalidomide, and that GIMEMA and Myeloma XI relied on the post-ASCT subgroups. However, when the results of the 4 trials were pooled in a meta-analysis the difference in overall survival was not statistically significant when the most appropriate approach was applied (random effects, crossover adjusted). The PBAC noted that updated data for the Myeloma XI study indicates a significant improvement in OS for the ITT population.
- 7.6 The PBAC noted that there were some key differences across the populations for the lenalidomide versus BSC trials, and compared with the potential PBS population. A range of different induction therapies were used, including lenalidomide, which is not currently available for induction treatment in Australia. The PBAC considered that while a benefit for lenalidomide maintenance treatment was observed for patients both with and without prior lenalidomide induction, there was some evidence to suggest better OS in patients who received lenalidomide induction. Therefore the magnitude of benefit observed in the trials may be greater than what would be realised in the Australian population.
- 7.7 The PBAC also noted that there were differences in the lenalidomide dosing regimens used across the four lenalidomide versus BSC trials. Only the CALGB trial used the dosage regimen recommended in the PI (starting dose of 10 mg/day increasing after 3 months to 15 mg/day if tolerated). Patients in IFM 2005-02 received 2 cycles of 25 mg/day lenalidomide post-ASCT, followed by 10 mg/day. GIMEMA and Myeloma XI both used a dose of 10 mg/day for 21 days of a 28 day cycle. Given the available clinical evidence, and that the FDA recommended dose is

10 mg/day, in Australian clinical practice the dose of lenalidomide may be increased to 15 mg/day in relatively few patients, particularly given that greater exposure to the drug may increase toxicities and the risk of secondary primary malignancy.

- 7.8 The PBAC considered that the claim of superior efficacy and inferior safety for lenalidomide compared to BSC was adequately supported by the evidence presented in the submission.
- 7.9 The PBAC considered that the lenalidomide versus BSC model presented in the submission would require some adjustments for any future resubmission. Specifically:
- The modelled time horizon of 25 years was too long, and the PBAC considered that a 15 year time horizon was more appropriate.
  - The use of fitted survival curves for the duration of the model was inappropriate, particularly given that the fitted survival curves were a poor fit for the lenalidomide Kaplan-Meier data, and this resulted in an overestimate of the incremental benefit in this period.
  - The lenalidomide dose, time on treatment and efficacy were sourced from different trials without consideration of the associated impact.
  - The utility values in the pre-progression state were higher for patients on lenalidomide treatment compared to those on BSC. This is inconsistent with the data presented, and the submission's clinical claim that lenalidomide has inferior safety compared to BSC.
  - For the lenalidomide treatment arm, a considerable proportion of the quality-adjusted life-years (QALYs) accrued prior to progression were from the 'pre-progression, off-treatment' state, which is inconsistent with lenalidomide being used until disease progression.

#### **Lenalidomide versus thalidomide**

- 7.10 The PBAC noted that the indirect comparison of lenalidomide to thalidomide presented in the submission was based on the CALGB and Myeloma IX trials. For PFS, there was no statistically significant difference for the two treatments even when the CALGB results were adjusted for cross-over. The impact of thalidomide on OS (i.e. the OS HR) was derived from the proportion alive at 3 years and assuming exponential distribution. The PBAC considered this approach to be unreliable and inadequately justified given the availability of alternative data sources. On the basis of the analysis presented, the submission claimed a statistically significant improvement in OS with lenalidomide compared with thalidomide maintenance. The PBAC considered that it was implausible that lenalidomide would increase OS compared with thalidomide, but have no impact on PFS, especially in the context of maintenance therapy where the aim of treatment is to extend the period of time in the progression-free state.

- 7.11 The PBAC noted two other potentially relevant trials identified during the evaluation (MM6 and Myeloma X), which were excluded by the submission, demonstrated a statistically significant benefit for thalidomide over BSC in PFS and for MM6 in OS. The PBAC further noted the 2012 IMWG consensus paper for maintenance therapy in MM included 7 thalidomide trials.
- 7.12 The PBAC considered that MM6 was a relevant trial, although noted it was conducted during an earlier time period compared with the lenalidomide maintenance trials. The PBAC further considered that substantial changes in patient care over this time, including differences in the induction regimens used, complicate the interpretation of the comparison with the lenalidomide results. However, the PBAC noted that the relative improvements in PFS and OS with thalidomide in MM6 were similar to those observed with lenalidomide with CALBG.
- 7.13 On balance, the PBAC considered that the evidence was insufficient to support a claim of superior efficacy for lenalidomide compared to thalidomide, and that a claim on non-inferiority may be more appropriate.
- 7.14 The PBAC considered that the claim of different safety may be reasonable, noting that while there is a strong patient preference for the lower rates of peripheral neuropathy experienced with lenalidomide when compared to thalidomide, lenalidomide is associated with other toxicities such as neutropenia and a higher risk of irreversible and potentially fatal secondary primary malignancy.
- 7.15 The PBAC considered, given the claim of superior efficacy for lenalidomide compared to thalidomide was inadequately supported by the evidence presented, that a cost-minimisation approach would be more appropriate than the cost-effectiveness model presented in the submission. Notwithstanding this issue, the PBAC agreed with the concerns raised during the evaluation and by the ESC with respect to the lenalidomide vs thalidomide model, as outlined in section 6.

### **Financial estimates**

- 7.16 The PBAC noted that most of issues raised by the DUSC with respect to the utilisation estimates had been addressed in the pre-PBAC response. However, the PBAC also noted that further adjustment to account for prevalent post-ASCT patients who haven't yet progressed that may switch to lenalidomide if it is PBS listed should be made in any future resubmission. The PBAC also considered that in the context of the high potential cost, a Risk Sharing Arrangement would be appropriate.
- 7.17 The PBAC would welcome a resubmission, and advised that any future submission should include:
- A cost-effectiveness analysis versus BSC and a cost-minimisation versus thalidomide, and a revised estimate for the proportion of expected replacement of these two therapies in the proposed treatment setting.
  - All relevant lenalidomide versus BSC randomised trials, including the updated

Myeloma XI data.

- All relevant thalidomide versus BSC randomised trials, and a justification for any RCTs excluded.
- Adjustments to the model for lenalidomide vs. BSC as outlined in paragraphs 7.9 and section 6.
- Adjustment to the financial estimates to account for patients who are post-ASCT but unprogressed at the time of PBS listing who may switch to lenalidomide from either thalidomide or BSC.
- A risk sharing arrangement.

7.18 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**

Lenalidomide is the only TGA registered therapy for maintenance in Australia. Celgene is committed to working with the PBAC and Department to make Lenalidomide available to Australian patients post autologous stem cell transplant.