7.07 LENALIDOMIDE, Capsule 5 mg, 10 mg and 15 mg, Revlimid®, Celgene Pty Ltd.

1 Purpose of Application

1.1 The resubmission requested a Section 100 (Highly Specialised Drugs) listing for lenalidomide monotherapy as maintenance treatment in patients with newly diagnosed multiple myeloma (NDMM) who have undergone an autologous stem cell transplant (ASCT). The key components of the resubmission are summarised in Table 1.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	NDMM patients who have undergone ASCT irrespective of conditioning regimen.
Intervention	Lenalidomide maintenance regimen (TGA approved): Lenalidomide 10 mg/day orally, increasing to 15 mg/day (after 3 months) if tolerated. Treatment should continue until disease progression or intolerance. Dosing may be modified (by level/frequency) based upon clinical and laboratory findings.
Comparator	[redacted]% - best supportive care (placebo as proxy): • Routine follow up post-ASCT (per MSAG Guidelines). • No active maintenance therapy. [redacted]% - thalidomide consolidation regimen: Thalidomide 100 mg/day orally +/- prednisolone 50 mg/alternate days. Treatment should continue for approximately 12 months or until disease progression or intolerance.
Outcomes	PFS, OS, PFS after next line therapy (PFS2) and response rate.
Clinical claim	In NDMM post-ASCT: • Lenalidomide has superior comparative efficacy (OS and PFS) and inferior comparative safety than BSC. • Lenalidomide has non-inferior OS and PFS and different safety to thalidomide.

ASCT = autologous stem cell transplant; BSC = best supportive care; MSAG = medical scientific advisory group; NDMM = newly diagnosed multiple myeloma; OS = overall survival; PFS = progression free survival; PFS2 = progression free survival after next line of therapy.
Source: Table 1-2, p.14 of the resubmission.

2 Requested listing

2.1 The details of the proposed published and effective prices are summarised in Table 2. The proposed effective prices under a revised Special Pricing Arrangement (SPA), which would apply only to use in maintenance post-ASCT, have been reduced by approximately [redacted]% from those in the March 2018 submission.

2.2 The revised effective prices were based on the weighted combination of lenalidomide prices used in the cost-utility analysis of lenalidomide and BSC and the prices resulting from the cost-minimisation analysis comparing lenalidomide with thalidomide.

Table 2: Proposed published and effective prices

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
Lenalidomide, Capsule, 5 mg	1	2	Published: $[redacted] (public) $[redacted] (private) Effective: $[redacted] (public) $[redacted] (private)	Revlimid® Celgene Pty Ltd
Lenalidomide, Capsule, 10 mg	1	2	Published: $[redacted] (public) $[redacted] (private) Effective: $[redacted] (public) $[redacted] (private)	Revlimid® Celgene Pty Ltd
Lenalidomide, Capsule, 15 mg	1	2	Published: $[redacted] (public) $[redacted] (private) Effective: $[redacted] (public) $[redacted] (private)	Revlimid® Celgene Pty Ltd

2.3 The abbreviated proposed listings for initial and continuing therapy are provided in Table 3 and Table 4. Secretariat suggestions are in strikethrough for deletions.

Table 3: Proposed PBS listing – initial treatment

Category/Program:	Section 100 – HSD
PBS indication:	Multiple Myeloma
Treatment phase:	Initial treatment
Restriction: **Section 100 (HSD)**	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	The treatment must be as monotherapy; AND Patient must have undergone an autologous stem cell transplant as part of frontline therapy for newly diagnosed multiple myeloma; AND Patient must not have progressive disease following autologous stem cell transplant

Source: Table 1-7, p.21 of the resubmission

Table 4: Proposed PBS listing – continuing treatment

Episodicity:	Chronic
Condition:	Multiple Myeloma
PBS indication:	Multiple Myeloma
Treatment phase:	Continuing treatment
Restriction: Section 100 (HSD)	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must have previously been authorised with a PBS prescription with this drug for the condition; AND Patient must not have demonstrated progressive disease; AND ~~Patient must not be receiving concomitant PBS-subsidised bortezomib, thalidomide, carfilzomib or its analogues; AND~~ The treatment must be as monotherapy.

Source: Table 1-8, p.23 of the resubmission

2.4 It was noted that dosing for NDMM patients who have undergone ASCT is continuous daily dosing, and that the request is for a new pack size of 28. Lenalidomide for RRMM and NDMM patients who are ineligible for ASCT is given from days 1 to 21 of a 28 day cycle and is currently listed on the PBS as packs of 21.

2.5 The resubmission added a restriction for patients on continuing treatment, decreased the number of repeats from five to two (allowing for 3 months treatment) and proposed that continuing scripts be accessed by telephone authority. The PBAC had previously considered it may be more appropriate to provide three months treatment per prescription, instead of six, as patients receiving lenalidomide maintenance treatment should be regularly reviewed by a medical practitioner. The PBAC also considered requesting initial prescriptions by written authority and continuing prescriptions by telephone authority to be reasonable (paragraph 2.5, Lenalidomide Public Summary Document (PSD), March 2018).

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

3 Background

Registration status

3.1 Lenalidomide was approved by the TGA on the 17th January 2018 for the new indication 'maintenance treatment of patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation'.

Previous PBAC consideration

3.2 A summary of the matters of concern raised with respect to the March 2018 submission, and how they have been addressed in the March 2019 resubmission is provided in Table 5.

Table 5: Summary of outstanding matters of concern

Component	Matter of concern by PBAC	How the resubmission addresses it
Clinical		
Comparator	A mixed comparator of thalidomide and BSC is reasonable, rather than the main comparator being BSC and supplementary comparator thalidomide. (paragraph 7.3, Lenalidomide PSD, March 2018)	Addressed: mixed comparator incorporating BSC ([redacted]%) and thalidomide ([redacted]%) estimated based on MRDM dataset.
Clinical evidence	Excluded a relevant thalidomide trial (MM6) and updated data from lenalidomide trial (Myeloma XI). (paragraph 7.5 & 7.12, Lenalidomide PSD, March 2018) Excluded seven thalidomide trials from the 2012 IMWG consensus paper for MM maintenance therapy. (paragraph 7.11, Lenalidomide PSD, March 2018)	Partially addressed: MM6 and Myeloma XI (updated data cut-off Sept-17) included (not in ITC). Adequate reasons provided for including two and excluding five of the trials.
Indirect comparison	Did not utilise ITT results from RCTs as excluded patients not undergoing ASCT. Approach to ITC (bespoke Bayesian fixed effects) inappropriate given trial heterogeneity. Implausible results for thalidomide: Improved OS, no difference PFS. Included only patients post-ASCT. (paragraph 7.4 & 7.5, Lenalidomide PSD, March 2018)	Addressed: Revised ITC (to include ITT) with sensitivity analysis for all patients and post-ASCT patients. Random effects model used. (Pairwise frequentist ITC using updated trials)
Clinical claim	Clinical claim of superiority to thalidomide inappropriate (superior OS, non-inferior PFS and different safety). (paragraph 7.14, Lenalidomide PSD, March 2018)	Addressed: Thalidomide claim revised to non-inferior efficacy and different safety.
Economic		
Approach to the economic analysis	Lack of support for a CEA compared with thalidomide (CMA more appropriate).	Addressed: CEA for lenalidomide with BSC; CMA for lenalidomide with thalidomide.
Time horizon	25 years was too long, and 15 years considered more appropriate. (paragraph 2.5, Lenalidomide PSD, March 2018)	Addressed: 15 years (vs 6 years in CALGB).
Basis of evidence in model	Used PFS and OS fitted curve for the entire time horizon (CALGB trial). (paragraph 6.40, Lenalidomide PSD, March 2018)	Modified as requested: OS and PFS were extrapolated from CALGB and applied to KM in the model from median follow-up (72 months).
Dose per cycle	Sourced from IFM2005-02 trial, since unavailable for CALGB. There is a mismatch between the assumed efficacy and the drug dose required to achieve it used within the economic evaluation. IFM2005-02 included a consolidation dose of lenalidomide 25 mg, and lower maintenance dose of 2.5 mg, in addition to 5 mg, 10 mg and 15 mg. (paragraph 6.42, Lenalidomide PSD, March 2018)	Not addressed. The ESC noted that the average daily dose of lenalidomide in IFM2005-02 was [redacted] mg. This was consistent with the recommended daily dose in the PI of 10 mg/day, increasing to 15 mg/day if tolerated, as the PBAC previously noted that relatively few patients would increase to 15 mg/day due to toxicity issues (paragraph 7.7, Lenalidomide PSD, March 2018).
Utilities	Unrealistic differential PF utility values, being higher for lenalidomide (lenalidomide 0.795, BSC at 0.780). This is inconsistent with the clinical claim. (paragraph 7.9, Lenalidomide PSD, March 2018)	Addressed: PF utilities in both treatment groups were assumed at 0.780.
Financial estimates		
Approach	Epidemiological approach, assuming [redacted] uptake rate with lenalidomide in post-ASCT setting for new patients only. Not incorporating prevalent patients who may switch from other therapy (thalidomide).	Partially addressed: epidemiological/market share approach adopting patient flow. Assuming [redacted]%

Component	Matter of concern by PBAC	How the resubmission addresses it
		uptake rate in new patients with lenalidomide.
Incidence rate	Based on ABMTRR Annual Data Summary 2013 and 2015, and growth rate of [redacted]%. (paragraph 6.60, Lenalidomide PSD, March 2018)	Partially addressed: based on Cancer Australia statistics website and growth rate of [redacted]%.
Prevalence rate	Did not include patients who are post-ASCT and have not yet progressed. (paragraph 7.16, Lenalidomide PSD, March 2018)	Addressed: updated based on approximation from 10% Medicare Australia sample data and other sources.
RSA	PBAC noted that due to high potential cost an RSA would be appropriate. (paragraph 7.16, Lenalidomide PSD, March 2018)	Partially addressed: indicated amendments to the current RSA for lenalidomide. However, no specific details were provided.

Source: Section 1 of the March 2018 submission and pre-PBAC response, Sections 1-4 of the resubmission. Compiled during evaluation.
ABMTRR = Australasian Bone Marrow Transplant Recipient Registry; ASCT = autologous stem cells transplant; AUC = area under a curve; BSC = best supportive care; CEA = cost effectiveness analysis; CMA = cost minimisation analysis; ITC = indirect trial comparison; ITT = intention to treat; OS = overall survival; PBS = Pharmaceutical Benefit Scheme; PF = progression free; PFS = progression-free survival; PSD = Public Summary Document; RSA = risk sharing agreement; RCT = randomised control trial; vs = versus

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 Lenalidomide is an immunomodulatory drug (IMiD). IMiDs have both immunomodulatory and anti-angiogenic properties which could confer anti-tumour and anti-metastatic effects.

4.3 Currently, patients with NDMM who are eligible will undergo an ASCT, with the potential for use of subsequent therapy to maintain the response achieved during transplant. This is the proposed population for the requested expanded listing of lenalidomide. Lenalidomide is the only medicine currently registered by the TGA for use as maintenance therapy post-ASCT for MM.

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

5 Comparator

5.1 In accordance with PBAC advice (paragraph 7.3, Lenalidomide PSD, March 2018), the resubmission proposed a mixed comparator of BSC and thalidomide, as there would be a proportion of patients who would not tolerate thalidomide. The resubmission proposed relative weights of [redacted]% and [redacted]% respectively based on the data from the Myeloma and Related Diseases Registry (MRDR). The Myeloma Scientific and Advisory Group (MSAG) guidelines indicated that although not always recommended, maintenance therapy with thalidomide is used in Australia for some patients.

5.2 The PBAC previously considered that there were some limitations with the MRDR data, particularly surrounding the completeness of this data set, quality control measures, and how missing data were accounted for (paragraph 5.3, Lenalidomide PSD, March 2018).

5.3 Data presented in the resubmission from the MRDR indicated that the proportion of NDMM patients who undergo an ASCT and do not receive active maintenance therapy ranged from [redacted]% to [redacted]% and that those receiving thalidomide-based therapies ranged from [redacted]% to [redacted]% depending on the patients included in the analysis and the definition of BSC.

5.4 When considering the March 2018 submission the PBAC considered that the proportion of patients receiving thalidomide post-ASCT was likely to be higher than that estimated by the MRDR. Clinician advice indicated that the use of thalidomide maintenance therapy has likely increased since the MRDR analysis, which was based on a sample of patients taken between 2012 and 2015 (paragraphs 5.3 and 7.3, Lenalidomide PSD, March 2018). In addition, advice from DUSC cited an analysis of the MRDR data by Bergin, 2017 which estimated the proportions of patients receiving BSC or thalidomide as 53.0% and 47.0% respectively (paragraph 6.61, Lenalidomide PSD, March 2018). The Pre-Sub-Committee Response (PSCR) and pre-PBAC response stated that Bergin (2017) is a brief conference abstract that reported limited data from an earlier analysis of a smaller cohort of patients (218 versus 301 patients) from the same registry than that used in the submission, and was therefore considered inferior. In the pre-PBAC response, the use of the updated MRDR analysis in preference to Bergin (2017) was also supported by Professor Andrew Spencer, one of the key authors of the Bergin abstract. The pre-PBAC response stated that it believed that the use of thalidomide post-ASCT was decreasing, not increasing, and was likely to be lower than that estimated by the MRDR, not higher, as stated by the PBAC in March 2018. The pre-PBAC response provided the following information to support the estimates provided in the resubmission:

- Analysis of the 10% PBS dataset indicated that thalidomide utilisation post-ASCT was decreasing over time. The pre-PBAC response states that in 2017 [redacted]% of patients who initiate induction with bortezomib went on to receive thalidomide, a decrease from [redacted]% in 2013/2014; and
- Advice from a Clinical Advisory Board was that the number of institutions using thalidomide maintenance had declined over the last few years and that there was no universal trend in the use of thalidomide post-ASCT.

5.5 The PBAC recalled that it had previously agreed with the ESC and DUSC in considering that Bergin, 2017 might better reflect thalidomide use. However, noting the arguments provided in the pre-PBAC response and considering the use of thalidomide outside of major teaching hospitals, agreed that thalidomide use in Bergin, 2017 might be overestimated. The PBAC considered that it would be more reasonable to assume a [redacted]% BSC and [redacted]% thalidomide weighing, which was calculated by excluding [redacted] BSC patients who were considered to be receiving active therapy from the MRDR

analysis (the resubmission classified BSC as including no maintenance therapy and maintenance therapy other than lenalidomide or thalidomide).

5.6 If used as post-ASCT maintenance therapy, the MSAG guidelines recommend thalidomide at a dose of 100 mg daily, with or without corticosteroids, for approximately 12 months.[1]

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (107), health care professionals (7) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with lenalidomide including improved overall survival, quality of life and tolerability, and fewer side effects than thalidomide.

6.3 The PBAC noted the advice received from the Leukaemia Foundation, Myeloma Australia and the Medical and Scientific Advisory Group (MSAG) of Myeloma Australia clarifying the likely use of lenalidomide in clinical practice. The PBAC specifically noted the advice that the use of lenalidomide may extend remission and would have fewer side effects than the currently used option (thalidomide). The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.4 The resubmission was based on four randomised lenalidomide trials. Two trials compared lenalidomide to placebo following ASCT (CALGB: N=460; IFM2005-02: N=614) and 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). The PBAC noted that updated data for Myeloma XI (Sept-17 cut-off) were presented as requested in the March 2018 consideration (paragraph 7.4, Lenalidomide PSD, March 2018).

6.5 As no head-to-head trials of lenalidomide and thalidomide were identified, an indirect comparison was conducted using two randomised trials comparing thalidomide to observation (Myeloma IX: N=493; MM6: N=112). The inclusion of MM6 was at the request of the PBAC (paragraph 7.11, Lenalidomide PSD, March 2018). For the comparison of thalidomide versus observation and for the indirect comparison with

[1] Medical Scientific Advisory Group to the Myeloma Foundation of Australia. Clinical Practice Guideline: Multiple Myeloma. V.4 Updated March 2017. Available at: http://myeloma.org.au/wp-content/uploads/2017/10/MSAG-Clinical-Practice-Guideline-Myeloma-V4-March-2017.pdf

lenalidomide (using evidence from CALGB), two alternative approaches to support the clinical claim were presented, based on (i) Myeloma IX alone (as per the March 2018 submission) or (ii) a meta-analysis of the Myeloma IX and MM6 trials. Details of the trials presented in the submission are provided in Table 6.

Table 6: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Lenalidomide		
CALGB NCT00114101	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
	BresMed. Adjustment for treatment crossover in the Cancer and Leukaemia Group B (CALGB) trial in multiple myeloma: Statistical analysis report	Feb 23 2017
	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 + Corrected Supplementary Appendix	*Lancet Haematol.* 2017; 4(9):e431-442
	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) crossover (XO)	*Journal of Clinical Oncology.* 2017; 35:15 Supplement 1
	McCarthy PL, Owzar K, Hofmeister CC et al. Analysis of overall survival (OS) in the context of crossover 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; 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
IFM2005-02 NCT00430365	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
	Attal M, Lauwers-Cances V, Marit G et al. Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma	*N Engl J Med.* 2012; 366: 1782-91
	Attal M, Lauwers-Cances V, Marit G et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma: Follow-up analysis of IFM2005-02	*Blood.* 2013; 122 (406)
	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 IFM2005-02	*Blood.* 2013; 122 (21)
	Attal M, Lauwers-Cances V, Marit G et al. Maintenance treatment with lenalidomide after transplantation for MYELOMA: Final analysis of the IFM2005-02	*Blood.* 2010; 116 (21)
GIMEMA NCT00551928	Palumbo A, Cavallo F, Gay F et al. Autologous Transplantation and Maintenance Therapy in Multiple Myeloma	*N Engl J Med.* 2014; 310(10):895-905
	Boccadoro M, Cavallo F, Gay F et al. Melphalan/prednisone/lenalidomide (MPR) versus high-dose melphalan and autologous transplantation	*Journal of clinical oncology.* 2013; 31(15 suppl. 1)

Trial ID	Protocol title/ Publication title	Publication citation
	(MEL200) plus lenalidomide maintenance or no maintenance in newly diagnosed multiple myeloma (MM) patients	
	Cavallo F, Gay F, Di Raimondo F, et al. Lenalidomide maintenance improves survival in newly diagnosed young multiple myeloma (MM) patients	*Haematologica.* 2013; 98:50
	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	*Haematologica.* 2012; 97: 472-473
	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	*Haematologica.* 2013, 98:96,
	Cavallo F, Gay F, Caravita di toritto T. Lenalidomide Maintenance Improves Progression Free Survival in Newly Diagnosed Young Multiple Myeloma (MM) Patients	*Clinical Lymphoma, Myeloma and Leukemia.* 2013; 13: S120
Myeloma XI NCT01554852	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	ASH 58th Annual Meeting and Exposition 2016, December 3-6; 1143
	Jackson GH, Davies FE, Pawlyn C et al. Lenalidomide Induction and Maintenance Therapy for Transplant Eligible Myeloma Subjects: Results of the Myeloma XI Study'	ASCO conference presentation 2017, abstract 8009
	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	*Blood.* 2015. 126 (23):1847
	Jones J, Pawlyn C, Brioli A et al. Myeloma XI trial-second primary malignancy interim report in newly diagnosed multiple myeloma (NDMM) patients	*Blood.* 2014; 124(21)
	Jackson et al. Lenalidomide maintenance significantly improves outcomes compared to observation irrespective of cytogenetic risk: results of Myeloma XI	*Blood.* 2017; 130(1)
	Bradbury C A, Jenner M W, Striha A et al. Thrombotic Events in Patients with Myeloma Treated with Immunomodulatory Drugs; Results of the Myeloma XI Study	*Blood. 2017; 130(1):553*
Thalidomide		
Myeloma IX ISRCTN68454111	Morgan G, Davies FE, Gregory WM et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis	*Blood.* 2012; 119(1):7-15
	Morgan G, Davies FE, Gregory WM et al. Long-term follow-up of MRC Myeloma IX trial: Survival outcomes with bisphosphonate and thalidomide treatment	*Clinical Cancer Research.* 2013; 19(21): 6030-38
	Morgan G, Davies FE, Gregory WM et al. Thalidomide maintenance significantly improves progression-free survival (PFS) and overall survival (OS) of myeloma patients when effective relapse treatments are used: MRC myeloma IX results'	*Blood.* 2010; 116 (21)
MM6	Spencer et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma subjects undergoing a single autologous stem-cell transplantation procedure.	*Journal of Clinical Oncology.* 2009; 27(11): 1788-93
	Kalff et al. Thalidomide and prednisolone versus prednisolone alone as consolidation therapy after autologous stem-cell transplantation in subjects with newly diagnosed multiple myeloma: Final analysis of the ALLG MM6 multicentre, open-label, randomised phase 3 study.	*The Lancet Haematology.* 2014; 1(3):e112-e119

Source: Table 2.2.1, p.40-42 of the submission and Table 2-2, p. 27 of the resubmission.

6.6 The key features of the randomised trials are summarised in Table 7.

Table 7: Key features of the included evidence – direct and indirect comparisons

Trial	N	Design	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Lenalidomide vs. placebo						
CALGB	460	R, DB	Low; crossover	Post-ASCT	PFS, OS, ORR, PFS2	OS, PFS, ToT, AE
IFM2005-02	614	R, DB	Low	Post-ASCT	PFS, OS, ORR, PFS2	OS, PFS sensitivity analysis, AE
GIMEMA	135[a]	R, OL	Low/unclear	ASCT and non-ASCT	PFS, OS, PFS2	OS, PFS sensitivity analysis, AE
Myeloma XI	788[a]	R, OL	Low/unclear	ASCT and non-ASCT	PFS	Patient level data were not available
Meta-analyses	-	CALGB (adjusted for crossover) / IFM2005-02 / GIMEMA (subgroup analysis) / Myeloma XI (Sept 17 cut-off data)				OS and PFS, sensitivity analyses
Thalidomide vs. BSC						
Myeloma IX	493[a]	R, OL	Low/unclear	ASCT and non-ASCT	PFS, OS	NA
MM6	243	R, OL	High/unclear[b]	Post-ASCT	PFS, OS	NA
Meta-analyses	-	Myeloma IX (subgroup analysis) / MM6				OS and PFS, sensitivity analyses
Lenalidomide vs. thalidomide						
Indirect comparison	Primary analysis: CALGB (adjusted for crossover) versus Myeloma IX (subgroup analysis) Sensitivity analyses: Lenalidomide meta-analyses versus thalidomide meta-analyses					OS and PFS, sensitivity analyses

AE = adverse events; ASCT = autologous stem cell transplant; DB = double blind; NA = not applicable; OL = open label; OS = overall survival; PFS = progression-free survival; PFS2 = progression free survival after next line of therapy; R = randomised; ToT = time on treatment.

a. Reported subgroups, Total population as follows: GIMEMA = 273; Myeloma XI = 1,550 and Myeloma IX= 820.

b. The resubmission stated MM6 had a "considerable risk" of bias, though it was unclear to the evaluators whether this trial had a greater risk of bias than the other randomised, open-label trials.

Source: Table 2.3.1, p.51-54 and Table 2.3.2, p.56-57 of the March-2018 submission. Section 2.5-2.6, p.80-127 of the March-2018 submission. Table 2-4, p.30 of the resubmission.

6.7 In CALGB, crossover occurred from the placebo arm to the lenalidomide arm after the trial was unblinded following the interim analysis. Crossover was only allowed for placebo patients who had not progressed. The comparative efficacy based on PFS and OS outcomes may be diluted by crossover, biasing against lenalidomide; the submission adjusted for this effect. The PBAC previously acknowledged that crossover in CALGB, and unblinding in IFM2005-02 may have diluted the treatment effect of lenalidomide (paragraph 7.5, Lenalidomide PSD, March 2018).

6.8 There were transitivity issues between the trials for lenalidomide. Only CALGB used the dosage regimen recommended in the approved PI (starting dose of 10 mg/day increasing after 3 months to 15 mg/day if tolerated); however, the mean daily dose in CALGB was not reported. The PBAC noted that Holstein, 2017 reported that the median dose for the duration of treatment for the lenalidomide group in CALGB was 6.8 mg per day (interquartile range: 4.6, 9.5). The PBAC previously noted that there would be relatively few patients increasing their dose to 15 mg/day in Australian clinical practice, particularly given that greater exposure to the drug may increase toxicities and the risk of secondary primary malignancy (paragraph 7.7, Lenalidomide PSD, March 2018). Patients in IFM2005-02 received 2 cycles of 25 mg/day lenalidomide post-ASCT, followed by an average of [redacted] mg/day. GIMEMA and Myeloma XI both used a dose of 10 mg/day for 21 days of a 28 day cycle. Due to these

differences in dosing regimen from CALGB, along with other differences in study conduct and trial populations, these trials (IFM2005-02, GIMEMA and Myeloma XI) were included by the resubmission in the meta-analyses and indirect comparisons as sensitivity analyses.

6.9 The GIMEMA, Myeloma XI and Myeloma IX trials also included NDMM patients who did not receive an ASCT but were randomised to maintenance therapy; the resubmission included analyses of ITT, ASCT and non-ASCT patients. This was in line with PBAC requests (paragraph 7.4, Lenalidomide PSD, March 2018).

6.10 MM6 data were included in the meta-analyses and indirect comparisons of lenalidomide and thalidomide as sensitivity analyses only as it was conducted in an earlier time period than the lenalidomide trials and due to the resubmission determining that it was affected by a high level of bias. This was based on the independent assessment of the results of MM6 by the Melbourne University Statistical Consulting Centre. Three potential issues in the Kalff, 2014 paper were identified:

(1) it was implausible that the PFS and OS HRs (0.16 and 0.12 respectively) could change so dramatically from those reported in Spencer (2009) (0.50 and 0.41 respectively);

(2) the analysis assumed 100% survival over the 8 to 12 months duration of treatment; and

(3) the confidence intervals for PFS and OS were too narrow given the number of subjects in the trial.

6.11 The ESC considered that the different treatment setting and potential statistical errors from the Kalff 2014 paper justified not combining the results from MM6 in meta-analyses with those from Myeloma IX; instead using MM6 in sensitivity analyses.

Comparative effectiveness

Lenalidomide vs. BSC

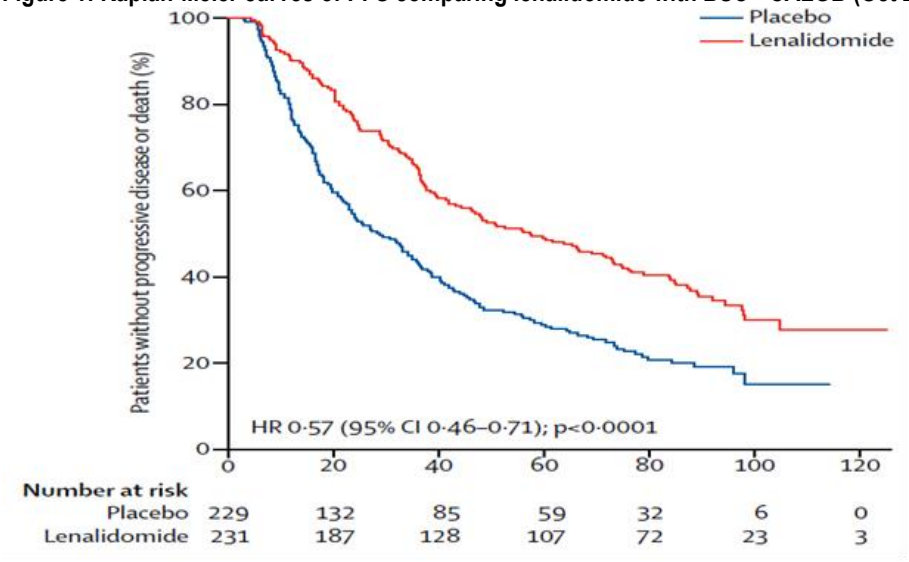
6.12 The results from CALGB and IFM2005-02 for PFS and OS are presented in Tables 8 and 9 (with the corresponding Kaplan-Meier data for CALGB in Figure 1 and Figure 2). While both trials showed a statistically significant improvement in PFS, only CALGB showed a statistically significant improvement in OS. The March 2018 submission argued that this was due to IFM2005-02 being underpowered to detect a difference in OS. The evaluators considered this reasonable. Additionally, the trial was unblinded after the interim analysis (July 2010).

Table 8: CALGB and IFM 2005 02 – PFS results – lenalidomide versus BSC

	Lenalidomide		BSC		Difference in median, months	Hazard ratio (95% CI)
	n/N (%)	Median PFS, months (95% CI)	n/N (%)	Median PFS, months (95% CI)		
CALGB						
Oct 2016[a]	146/231 (63%)	57.3 (44.2, 73.3)	176/229 (77%)	28.9 (23.0, 36.3)	28.4	**0.57 (0.46, 0.71)**
IFM2005-02						
Feb 2016[b]	218/307 (71.0%)	44.4 (39.6, 52.0)	257/307 (83.7%)	23.8 (21.2, 27.3)	20.6	**0.57 (0.47, 0.68)**

ASCT = autologous stem cell transplant; BSC = best supportive care; CI = confidence interval; PFS = progression-free survival
a. From ASCT;
b. From maintenance randomisation.
Statistically significant differences bolded.
Source: Table 2.5.1, p.80 of the March-2018 submission.

Figure 1: Kaplan-Meier curves of PFS comparing lenalidomide with BSC - CALGB (Oct 2016 cut-off)



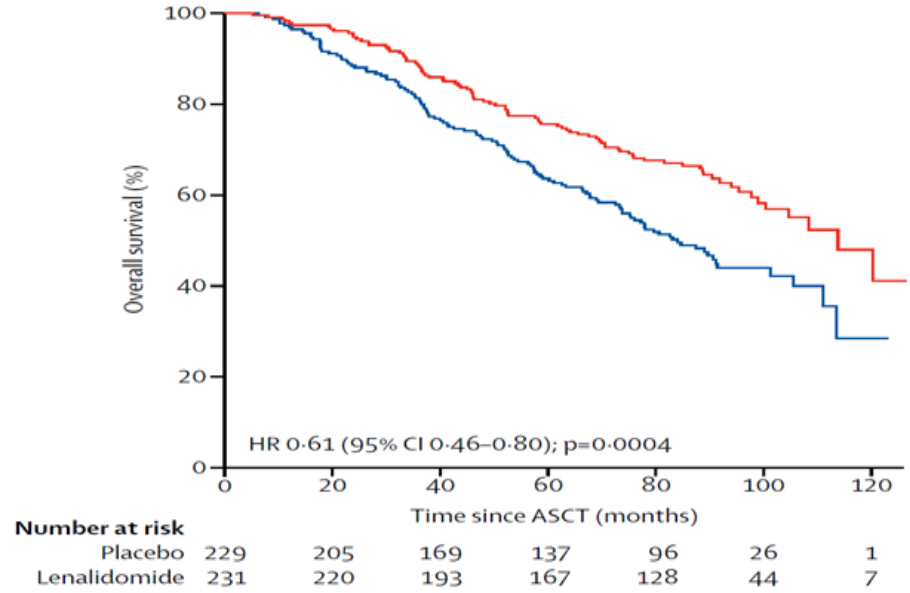
ASCT = autologous stem cell transplant; CI = confidence interval; HR = hazard ratio; PFS = progression-free survival
Notes: PFS was measured as time since ASCT according to EMA censoring rules (months). Trial refers to placebo, have used best supportive care for consistency.
Source: Figure 2.5.1, p.82 of the March-2018 resubmission.

Table 9: CALGB and IFM2005 02 – OS results – lenalidomide versus BSC

	Lenalidomide		BSC		Difference in median, months	Hazard ratio (95% CI)
	n/N (%)	Median OS, months (95% CI)	n/N (%)	Median OS months (95% CI)		
CALGB						
Oct 2016[a]	88/231 (38.1%)	113.8 (100.4, NE)	120/229 (52.4%)	84.1 (73.8, 106.0)	29.7	**0.61 (0.46, 0.80)**
IFM2005-02						
Feb 2016[b]	143/307 (46.6%)	105.9 (88.8, NE)	160//307 (52.1%)	88.1 (80.7, 108.4)	17.8	0.90 (0.72, 1.13)

ASCT = autologous stem cell transplant; BSC = best supportive care; CI = confidence interval; NE = not evaluable; 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.
Some figures are corrected from submission and proportions presented to 1 decimal point. Statistically significant differences bolded.
Source: Table 2.5.3, p.85-86 of the March-2018 submission.

Figure 2: Kaplan-Meier curve of OS of lenalidomide compared with BSC - CALGB (Oct 2016 cut-off)



ASCT = autologous stem cell transplant; CI = confidence interval; HR = hazard ratio; OS = overall survival.
Notes: OS is measured as time since ASCT (months). Trial refers to placebo, have used best supportive care for consistency.
Source: Figure 2.5.4, p.86 of the March-2018 submission.

6.13 The PFS and OS results for the post-ASCT subgroups in GIMEMA and Myeloma XI (including updated data for the Sept-17 cut-off) are presented in Tables 10 and 11, and Figures 3 and 4. No Kaplan-Meier curves were presented for the post-ASCT subgroup in GIMEMA. There were statistically significant improvements in PFS for lenalidomide versus BSC for the post-ASCT subgroup in GIMEMA and Myeloma XI. There were no statistically significant improvements in OS for lenalidomide versus BSC in the post-ASCT subgroups in GIMEMA or Myeloma XI.

Table 10: GIMEMA and Myeloma XI – Results of subgroup analyses with whole trial population results and complement results – PFS – lenalidomide versus BSC

	Lenalidomide		BSC		Difference in median, months	Hazard ratio (95% CI)
	n/N (%)	Median PFS, months (95% CI)	n/N (%)	Median PFS, months (95% CI)		
GIMEMA						
Whole (Apr 2013)	NR	41.9	NR	21.6	20.3	**0.48 (0.35, 0.68)[a]**
Post-ASCT subgroup (Apr 2013)	NR	NR	NR	NR	NR	**0.42 (0.24, 0.73)**
Complement (Apr 2013)	NR	NR	NR	NR	NR	**0.43 (0.28, 0.67)**
Mar 2015‑ASCT subgroup	NR	NR	NR	NR	NR	**0.52 (0.33, 0.82)**
Myeloma XI (cut-off unspecified)						
Whole	NR	36 (31, 39)	NR	18 (16, 20)	18	**0.45 (0.39, 0.52)**
ASCT subgroup	118/451 (26.1%)	50 (44, NE)	185/377 (54.9%)	28 (23, 32)	22	**0.47 (0.38, 0.60)**
Complement	NR	24 (21, 30)	NR	11 (9, 13)	13	**0.42 (0.35, 0.51)**
Myeloma XI – (cut-off September 2017)						
Whole	NR/1,137	38.9	NR/834	20.0	18.9	**0.46 (0.41, 0.53)**
ASCT subgroup	NR/1,137	56.9	NR/834	30.1	26.8	**0.48 (0.40, 0.58)**
Complement	NR/1,137	26.0	NR/834	11.0	15.0	**0.44 (0.37, 0.53)**

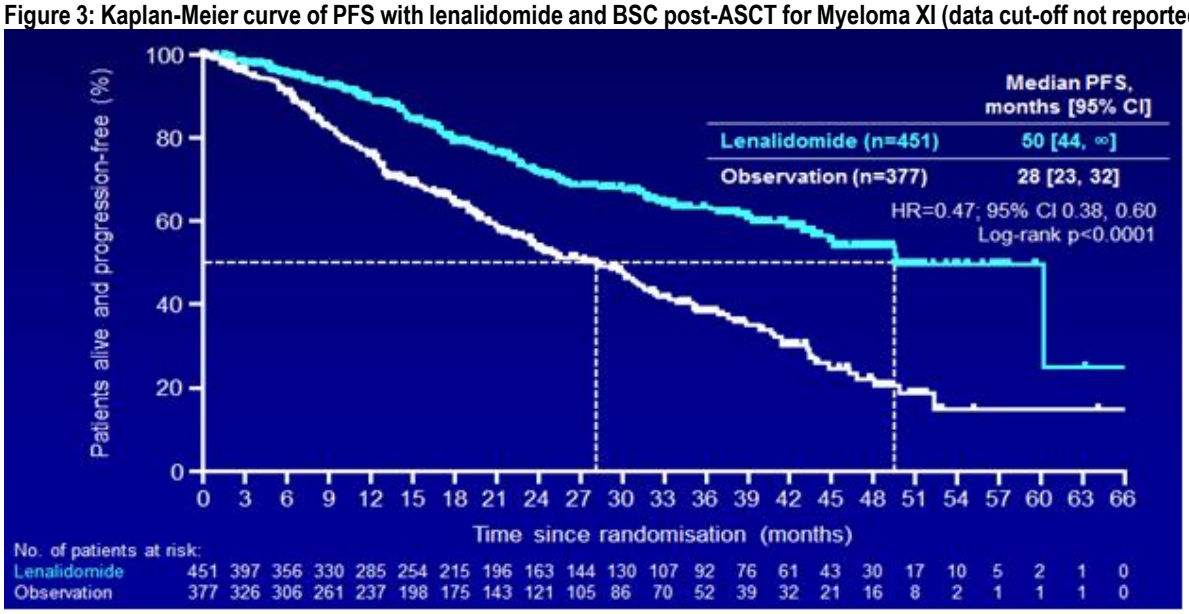
ASCT = autologous stem cell transplant; BSC = best supportive care; CI = confidence interval; HR = hazard ratio; NE = not evaluable; NR = not reported; PFS = progression free survival

a. Overall trial results differ in Figure S2B (HR = 0.48; 95% CI: 0.35, 0.68) than in the text (HR = 0.47; 95% CI: 0.33. 0.65; p901) in Palumbo et al. (2014).

Statistically significant differences bolded.

Source: Table 2.5.1, p.80, Table 2.6.1, p.108 & Figure 2.6.1, p.109 of the March 2018 submission, Table 2-3, p.28 of the resubmission, Slide 3 of Attachment 5 of the resubmission (Jones and Jackson (ASH 2017)).

Figure 3: Kaplan-Meier curve of PFS with lenalidomide and BSC post-ASCT for Myeloma XI (data cut-off not reported)



ASCT = autologous stem cell transplant; BSC = best supportive care; CI = confidence interval; HR = hazard ratio; PFS = progression-free survival

Note: PFS is measured as time since maintenance randomisation (months); censoring rules not reported.

Source: Figure 2.5.3, p.84 of the March 2018 submission.

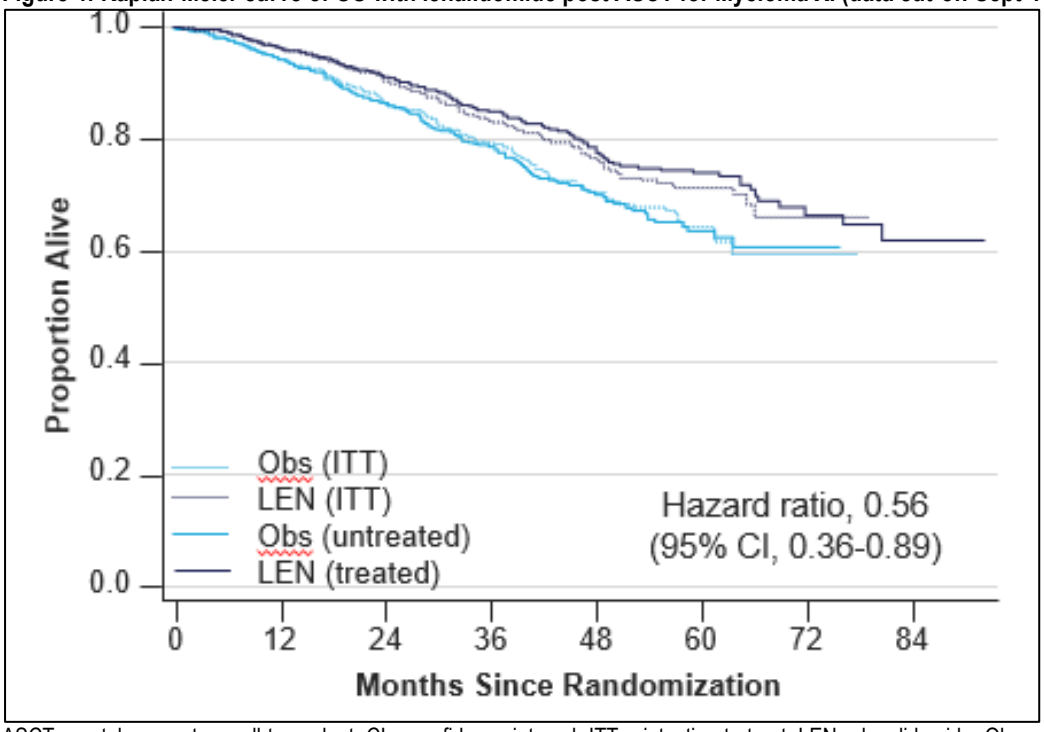
Table 11: GIMEMA and Myeloma XI – Results of subgroup analysis – OS – lenalidomide versus BSC

Trial ID	Lenalidomide		BSC		Hazard ratio (95% CI)
	n/N (%)	Median OS, months (95% CI)	n/N (%)	Median OS, months (95% CI)	
GIMEMA					
Apr 2013 - Whole	NR	NR (3-yr OS 88.0%)	NR	NR (3-yr OS 79.2%)	0.67 (0.38, 1.21)[a]
Apr 2013 - ASCT subgroup	NR	NR	NR	NR	0.62 (0.24, 1.59)
Apr 2013 - Complement	NR	NR	NR	NR	0.68 (0.32, 1.45)
Mar 2015 - Whole	NR	NR	NR	NR	NR
Mar 2015 - ASCT subgroup	15/67 (22.4%)	68.5 (66.9, NE)	23/68 (33.8%)	NR (61.9, NE)	0.66 (0.34, 1.26)
Mar 2015 - Complement	NR	NR	NR	NR	NR
Myeloma XI		**3-year rate, %**		**3-year rate, %**	
Whole (Sept-2017)	NR (21.4%)	78.6%	NR (24.2%)	75.8%	0.87 (0.73, 1.05)
ASCT subgroup (Sept-2017)	NR (12.5%)	87.5%	NR (19.8%)	80.2%	0.69 (0.52, 0.93)
Complement (Sept-2017)	NR (49.2%)	50.8%	NR (42.8%)	57.2%	1.02 (0.80, 1.29)

ASCT = autologous stem cell transplant; BSC = best supportive care; NE = not evaluable; NR = not reported; OS = overall survival

Source: Table 2.5.2 p.85 and Table 2.6.2, p.110 of the March 2018 submission, Table 2-3, p.28 of the resubmission, Slide 4 of Attachment 5 of the resubmission (Jones and Jackson (ASH 2017)), Morgan 2012; and calculated from source data

Figure 4: Kaplan-Meier curve of OS with lenalidomide post ASCT for Myeloma XI (data cut-off Sept-17)



ASCT = autologous stem cell transplant; CI = confidence interval; ITT = intention-to-treat; LEN = lenalidomide; Obs = observation; OS = overall survival; PFS = progression-free survival.
Note: PFS is measured as time since maintenance randomisation (months); censoring rules not reported.
Source: Slide 7 of Attachment 5 of the resubmission (Jones and Jackson (ASH 2017)).

Thalidomide vs. BSC

6.14 The results for the post-ASCT subgroup for thalidomide in Myeloma IX for PFS and OS are presented in Tables 12 and 13. No Kaplan-Meier curves were presented for the post-ASCT subgroup in Myeloma IX. There was a statistically significant improvement in favour of thalidomide in the post-ASCT subgroup for PFS but not for OS in Myeloma IX.

Table 12: Myeloma IX – Results of post-ASCT subgroup analysis – PFS – thalidomide versus BSC

Trial ID	Thalidomide		BSC		Difference in median, months	Hazard ratio (95% CI)
	n/N (%)	Median PFS, months (95% CI)	n/N (%)	Median PFS, months (95% CI)		
Myeloma IX (October 2009)						
Whole	NR	23 (NR)	NR	15 (NR)	8	**0.69 (0.58, 0.82)**
ASCT	NR	30 (NR)	NR	23 (NR)	7	**0.70 (0.56, 0.88)**
Complement	NR	11 (NR)	NR	9 (NR)	2	**0.74 (0.58, 0.94)**
Myeloma IX (Jan 2012) – median follow-up: 70.8 months						
Whole	NR	22 (NR)	NR	15	7	**0.69 (0.58, 0.82)**

ASCT = autologous stem cell transplant; BSC = best supportive care; C I =confidence interval; HR = hazard ratio; NA = not applicable; NR = not reported; PFS = progression free survival

Notes: There were no results reported for the ASCT and Complement sub-groups in the Jan-2012 data cutoff. Inverse HR reported in submission. Statistically significant differences bolded.

Source: Table 2.5.1, p.80, Table 2.6.1, p.108 & Figure 2.6.1, p.109 of the March 2018 submission. p.10 Morgan 2012. Myeloma IX data (Jan-2012) extracted from Morgan 2013.

Table 13: Myeloma IX – Results of subgroup analysis – OS – thalidomide versus BSC

	Thalidomide		BSC		Difference in median, months	Hazard ratio (95% CI)
	n/N (%)	Median OS, months (95% CI)	n/N (%)	Median OS, months (95% CI)		
Myeloma IX (October 2009) – median follow-up: 38 months						
Whole	NR	NR	NR	NR	NR	1.10 (0.85, 1.35)
ASCT	NR	NR (3-yr OS 75%)	NR	NR (3-yr OS 80%)	NR	NR
Complement	NR	38	NR	39	-1	1.00 (0.72, 1.37)
Myeloma IX (Jan 2012) – median follow-up: 70.8 months						
Whole	NR	60	NR	60	0	1.04 (0.85, 1.27)

ASCT = autologous stem cell transplant; BSC = best supportive care; Ci = confidence interval; HR = hazard ratio; NA = not applicable; NR = not reported; OS = overall survival.

Note: There were no results reported for the ASCT and Complement sub-groups in the Jan-2012 data cutoff. Inverse HR reported in submission. Statistically significant differences bolded.

Source: Table 2.5.1, p.80, Table 2.6.1, p.108 & Figure 2.6.1, p.109 of the March 2018 submission. p.10 Morgan 2012. Myeloma IX data (Jan-2012) extracted from Morgan 2013.

6.15 The PFS and OS results for MM6 are presented in Table 14. A statistically significant improvement in PFS and OS in favour of thalidomide was noted at both analysis time points (3-years and 5-years).

Table 14: MM6 – Summary of survival outcomes – thalidomide versus BSC

	Thalidomide N = 114	BSC N = 129	Absolute difference	HR (95% CI)
Progression-free survival				
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	**0.50 (0.35, 0.71)**
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	**0.16 (0.04, 0.58)**
Overall survival				
3-year follow-up				
Patients with event, n/N (%)	86%	75%	11%	
Median OS, months (95% CI)	-	-	-	**0.41 (0.22, 0.76)**
5.4-year follow-up				
Patients with event, n/N (%)	-	-	-	-
Median OS, months (95% CI)	102.0 (88.8, 116.4)	54.0 (46.8, 61.2)	48.0	**0.12 (0.03, 0.56)**

BSC = best supportive care; CI = confidence interval; HR = hazard ratio; IQR = inter-quartile range; OS = overall survival; PFS = progression free survival

Note: Spencer 2009 reported median PFS in days, this was converted into months. Kalff 2014 reported median PFS and OS in years, this was converted into months. Median follow-up in Kalff 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: Table 2-6 and Table 2.7, p.33 of the resubmission, Spencer 2009 and Kalff 2014.

6.16 The resubmission noted that the PFS and OS results for thalidomide versus BSC differed markedly between Myeloma IX and MM6.

Lenalidomide vs. BSC and thalidomide vs. BSC meta-analyses

6.17 An updated random effects meta-analysis of the lenalidomide (CALGB, IFM2005-02, GIMEMA and Myeloma XI) and thalidomide (Myeloma IX and MM6) trial data was presented in the resubmission. The PBAC previously considered it preferable and appropriate to consider the totality of the evidence rather than rely on evidence from one trial – CALGB (paragraph 6.18, Lenalidomide, PSD March 2018).

6.18 The meta-analyses used data from various cut-off dates and therefore the studies reflect different durations of exposure and durations of follow-up that may confound the ability to combine outcomes across trials. The pooled analyses also included a crossover adjustment in CALGB adopting a random effects approach. The PBAC has previously noted that using this approach resulted in a non-significant improvement in OS (paragraph 6.20, Lenalidomide, PSD March 2018).

6.19 The resubmission presented two sets of analyses for each therapy: one only included results for the post-ASCT subgroup in trials with mixed populations (as per the requested restriction); and one including results for all patients from these trials. This was in line with the PBAC request (paragraph 7.4, Lenalidomide, PSD, March 2018). The resubmission stated that the results of these analyses were generally similar at least with respect to the combined estimates of the hazard ratios (HR). The lenalidomide analysis also presented the results for ITT, PP and crossover adjusted analyses from CALGB. While the confidence intervals for these HR overlapped, there were differences in their point estimates.

6.20 The results of the meta-analyses (Table 15) showed a statistically significant improvement in PFS for lenalidomide. The OS HR in Myeloma XI was derived from the proportion alive at 3 years and assuming exponential distribution. The PBAC has previously considered this approach to be unreliable (paragraph 7.10, Lenalidomide PSD, March 2018). Nonetheless, the combined OS results were statistically significant in favour of lenalidomide compared with BSC.

Table 15: Results of the meta-analyses of lenalidomide trials (all subjects)

	Lenalidomide	Placebo/Observation	Comparison[a]
Progression free survival			
Individual trial results	**Median, months (95% CI)**	**Median, months (95% CI)**	**HR (95% CI)**
CALGB (ITT)	56.9 (41.9, 71.7)	29.4 (20.7, 35.5)	**0.61 (0.48, 0.76)**
CALGB (Adj)	[redacted]	[redacted]	[redacted]
CALGB (PP)	[redacted]	[redacted]	[redacted]
IFM2005-02	44.4 (39.6, 52)	23.8 (21.2, 27.3)	**0.57 (0.47, 0.68)**
GIMEMA	41.9 (NA)	21.6 (NA)	**0.48 (0.35, 0.68)**
Myeloma XI	38.9 (NA)	20.0 (NA)	**0.46 (0.41, 0.53)**
Meta-analysis results	**Model**	**Heterogeneity**	**HR (95% CI)**
Combined HR (ITT)	random effects	[redacted]	[redacted]
Combined HR (Adj)	random effects	[redacted]	[redacted]
Combined HR (PP)	random effects	[redacted]	[redacted]
Overall survival			
Individual trial results	**Median, months (95% CI)**	**Median, months (95% CI)**	**HR (95% CI)**
CALGB (ITT)	113.8 (100.4, NE)	84.1 (73.8, 106.0)	**0.61 (0.46, 0.80)**
CALGB (Adj)	[redacted]	[redacted]	[redacted]
CALGB (PP)	[redacted]	[redacted]	[redacted]
IFM2005-02	105.9 (88.8, NE)	88.1 (80.7, 108.4)	0.90 (0.72, 1.13)
GIMEMA	68.5 (66.9, NE)	NR (61.9, NE)	0.67 (0.38, 1.21)
Myeloma XI	3y OS: 87.5%	3yr OS: 80.2%	0.87 (0.73, 1.05)
Meta-analysis results	**Model**	**Heterogeneity**	**HR (95% CI)**
Combined HR (ITT)	random effects	[redacted]	[redacted]
Combined HR (Adj)	random effects	[redacted]	[redacted]
Combined HR (PP)	random effects	[redacted]	[redacted]

Adj = adjusted for crossover; CI = confidence interval; HR = hazard ratio; ITT = intention to treat; NA = not available; NE = not estimable; OS = overall survival; PP = per protocol.

Notes: Statistically significant differences bolded.

Source: Table 2-10, p.37 and Excel workbook, Attachment 6 of the resubmission. CALGB and IFM2005-02 used Feb 2016 cut-off date; GIMEMA: April 2013 cut-off; Myeloma XI: Sep 2017 cut-off.

6.21 The PFS results were statistically significant for thalidomide (ITT) in both the Myeloma IX and MM6. Only the MM6 showed statistically significant improvements in OS, the reported HR at 5 years follow-up was 0.12 (95% CI: 0.03, 0.56). The combined effects of pooling of the trial showed no statistically significant improvement in either PFS or OS for thalidomide (Table 16). The PBAC noted that due to the substantial differences in outcomes between the two thalidomide trials, the reliability of the pooled results was uncertain.

Table 16: Results of the meta-analyses of thalidomide trials (all subjects)

	Thalidomide	Placebo/Observation	Comparison
Progression free survival			
Individual trial results	**Median, months (95% CI)**	**Median, months (95% CI)**	**HR (95% CI)**
Myeloma IX	22	15	**0.69 (0.59, 0.82)**
MM6	32.4 (25.2, 38.4)	18.0 (13.2, 21.6)	**0.16 (0.04, 0.58)**
Meta-analysis results	**Model**	**Heterogeneity**	**HR (95% CI)**
Combined	random effects	I^2 = 79%; p = 0.03	0.38 (0.09, 1.56)
Overall survival			
Individual trial results	**Median, months (95% CI)**	**Median, months (95% CI)**	**HR (95% CI)**
Myeloma IX (Jan 2012 cutoff: 71 months)	60	60	1.04 (0.85, 1.27)
MM6 (60 months Kalff 2014)	102.0 (88.8, 116.4)	54.0 (46.8, 61.2)	**0.12 (0.03, 0.56)**
Meta-analysis results	**Model**	**Heterogeneity**	**HR (95% CI)**
Combined	random effects	I^2 = 87%; p = 0.006	0.41 (0.05, 3.31)

CI = confidence interval; HR = hazard ratio
Source: Table 2-12, p39, of the resubmission.

6.22 The results of the ITT meta-analyses for lenalidomide and thalidomide were replicated for the post-ASCT subgroups; overall there was a statistically significant difference in PFS and OS in favour of lenalidomide compared with BSC, but there was no statistically significant difference in PFS or OS for thalidomide compared with BSC.

Lenalidomide vs. thalidomide indirect comparison

6.23 The resubmission presented an indirect comparison between lenalidomide and thalidomide using placebo/observation as the common reference arm. The resubmission used a standard frequentist indirect comparison (Bucher) method. The results of the indirect comparison of CALGB and Myeloma IX in the post-ASCT population for PFS and OS are presented in Table 17. The resubmission also presented data for the indirect comparison of the ITT populations.

6.24 For PFS, there was no statistically significant difference between the two treatments even when the CALGB results were adjusted for crossover, with an estimated HR of [redacted] (95% CI: [redacted], [redacted]). The OS results showed a statistically significant improvement for lenalidomide compared to thalidomide with a HR of [redacted] (95% CI: [redacted], [redacted]).

6.25 The resubmission presented sensitivity analyses using a pooled analysis of all the lenalidomide trials (IFM2005-02, GIMEMA and Myeloma XI) and thalidomide trials (Myeloma IX and MM6). For the sensitivity analysis including all trials with CALGB adjusted for crossover (Sensitivity analysis 3), the difference in PFS was not statistically significant (HR = [redacted]; 95% CI: [redacted], [redacted]). Similarly, for OS the result was not statistically significant HR = [redacted]; 95% CI: [redacted], [redacted]). The upper bound on the confidence interval in the pooled sensitivity analyses has increased compared to the base case indirect comparison, reflecting the differences in results across the included trials.

Table 17: Results of the indirect comparisons between lenalidomide and thalidomide (post-ASCT subgroup)

Comparison	Trial /Analysis	HR (95% CI)
Progression free survival		
Lenalidomide v. Placebo/BSC	Pooled (CALGB ITT; IFM2005-02; GIMEMA; Myeloma XI)	**0.55 (0.49, 0.61)**
	Pooled (CALGB Adj; IFM2005-02; GIMEMA; Myeloma XI)	[redacted]
	Pooled (CALGB PP; IFM2005-02; GIMEMA; Myeloma XI)	[redacted]
Thalidomide v. Placebo/BSC	Myeloma IX	**0.70 (0.56, 0.88)**
	Pooled (Myeloma IX; MM6)	0.39 (0.09, 1.59)
Lenalidomide v. thalidomide	Base case: CALGB (Adj) vs Myeloma IX	[redacted]
	Sensitivity 1: CALGB (ITT) vs Myeloma IX	0.87 (0.63, 1.20)
	Sensitivity 2: CALGB (PP) vs Myeloma IX	[redacted]
	Sensitivity 3: All trials (Adj)	[redacted]
	Sensitivity 4: All trials (ITT)	1.41 (0.34, 5.77)
	Sensitivity 5: All trials (PP)	[redacted]
Overall survival		
Lenalidomide v. Placebo/BSC	Pooled (CALGB ITT; IFM2005-02; GIMEMA; Myeloma XI)	**0.73 (0.59, 0.89)**
	Pooled (CALGB Adj; IFM2005-02; GIMEMA; Myeloma XI)	[redacted]
	Pooled (CALGB PP; IFM2005-02; GIMEMA; Myeloma XI)	[redacted]
Thalidomide v. Placebo/BSC	Myeloma IX	1.29 (0.91, 1.83)
	Pooled (Myeloma IX; MM6)	0.44 (0.04, 4.50)
Lenalidomide v. thalidomide	Base case: CALGB (Adj) vs Myeloma IX	[redacted]
	Sensitivity 1: CALGB (ITT) vs Myeloma IX	**0.47 (0.30, 0.74)**
	Sensitivity 2: CALGB (PP) vs Myeloma IX	[redacted]
	Sensitivity 3: All trials (Adj)	[redacted]
	Sensitivity 4: All trials (ITT)	[redacted]
	Sensitivity 5: All trials (PP)	[redacted]

Adj = adjusted for crossover; BSC = best supportive care; CI = confidence interval; HR = hazard ratio; ITT = intention to treat
Note: CALGB and IFM2005-02(Feb 2016 data cut-off); GIMEMA (Mar 2015 data cut-off); Myeloma XI (Sep 2017 data cut-off); Myeloma IX (Oct 2009 data cut-off); MM6 (Dec 2012 data cut-off)
Source: Table 2-16, p.43 of the resubmission.

Comparative harms

6.26 A summary of the adverse events (AEs) and occurrence of second primary malignancies (SPMs) in the randomised trials CALGB and IFM2005-02 is presented in Tables 18 and 19. 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 18: Summary of key Grade 3 or 4 treatment-emergent adverse events in the key lenalidomide versus BSC randomised trials

Trial ID	LEN, n with event (%)	BSC (before XO), n with event (%)	BSC (after XO), n with event (%)	RR (95% CI)	RD (95% CI)
CALGB (March 2015)	**N = 224**	**N = 221**	**N = 76**		
Haematological					
Neutropenia	133 (59.4%)	73 (33.0%)	29 (38.2%)	**1.80 (1.45, 2.23)**	**26% (17%, 35%)**
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%)	**2.02 (1.26, 3.24)**	**10% (4%, 17%)**
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%)	**9.37 (2.21, 39.76)**	**8% (4%, 11%)**
Pneumonia	15 (6.7%)	4 (1.8%)	1 (1.3%)	**3.70 (1.25, 10.97)**	**5% (1%, 9%)**
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%)	**2.30 (1.08, 4.91)**	**5% (1%, 10%)**
IFM2005-02 (March 2015)	**N = 306**	**N = 302**			
Haematological					
Neutropenia	158 (53.9%)	21 (7.5%)	-	**7.19 (4.70, 11.00)**	**49% (42%, 56%)**
Leukopenia	71 (24.2%)	5 (1.8%)	-	**13.57 (5.56, 33.11)**	**24% (18%, 30%)**
Thrombocytopenia	38 (13.0%)	8 (2.9%)	-	**4.54 (2.16, 9.56)**	**13% (7%, 19%)**
Non-haematological					
Bronchitis	139 (47.4%)	104 (37.1%)	-	**1.28 (1.05, 1.55)**	**10% (2%, 18%)**
Diarrhoea	114 (38.9%)	34 (12.1%)	-	**3.20 (2.27, 4.53)**	**27% (20%, 34%)**
Fatigue	31 (10.6%)	15 (5.4%)	-	**1.97 (1.09, 3.58)**	**5% (1%, 10%)**
Nausea	31 (10.6%)	28 (10%)	-	1.06 (0.65, 1.72)	1% (-4%, 6%)
Lung disorder	19 (6.5%)	3 (1.1%)	-	**6.05 (1.81, 20.23)**	**8% (4%, 12%)**

BSC = best supportive care; CI = confidence interval; LEN = lenalidomide; PBO = placebo; RD = risk difference; RR = relative risk; XO = crossover

Source: Table 2.5.8, p.93-94 and Table 2.5.11, p.96-97 of the March-2018 submission.

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

Table 19: Secondary primary malignancies with maintenance therapy across the key lenalidomide versus BSC trials

	CALGB			RR	IFM2005-02		RR
	LEN	BSC			LEN	BSC	
Mar 2015	**N = 224**	**N = 221**			**N = 306**	**N = 302**	
SPM	42[b] (18.8%)	24[b] (10.9%)		**1.73 (1.08, 2.75)**	49[d] (16%)	27[d] (9%)	**1.79 (1.15, 2.79)**
Haematological	15 (6.7%)	8 (3.6%)		1.85 (0.80, 4.28)	21 (6.9%)	9 (3%)	**2.30 (1.07, 4.95)**
Solid tumour	17[c] (7.6%)	10[c] (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)
		Before XO	**After XO**				
Oct 2016	**N = 224**	**N = 143**	**N = 86**		**N = 306**	**N = 302**	
SPM	NR	NR	NR	-	51[b] (16.7%)	33[b] (10.9%)	**1.53 (1.01, 2.29)**
Haematological	18 (7.8%)	3 (2.1%)	0	**3.83 (1.15, 12.77**)	21[c] (6.9%)	9 (3%)	**2.30 (1.07, 4.95)**
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)

BSC = best supportive care; LEN = lenalidomide; NR = not reported; PBO = placebo; RR = relative risk; SPM = second primary malignancy; XO = crossover.

a. RR calculated during the evaluation for events in the PBO group up to the point of crossover 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 March-2018 submission.

6.27 Relative to BSC, the relevant safety outcomes for patients taking thalidomide were peripheral neuropathy and constipation. The overall incidence of events in MM6 is reported in Table 20.

Table 20: Overall incidence of adverse events ≥ 5% in any treatment group in MM6 – thalidomide versus BSC

	Total events			Grade 3 or 4		
	THAL n (%)	Control n (%)	RR^ (95% CI)	THAL n (%)	Control n (%)	RR^ (95% CI)
N	**114**	**129**		**114**	**129**	
Neuropathy	59 (52%)*	1 (< 1%)	66.7 (9.4, 474.2)	11 (10%)*	0	-
Infection	26 (23%)	20 (16%)	1.5 (0.9, 2.5)	12 (11%)	12 (8%)	1.1 (0.5, 2.4)
Weight gain	18 (16%)	14 (11%)	1.5 (0.8, 2.8)	2 (2%)	1 (< 1%)	2.3 (0.2, 24.6)
Mood alteration	17 (15%)	9 (7%)	2.1 (1.0, 4.6)	1 (< 1%)	3 (2%)	0.4 (0.0, 3.6)
Constipation	20 (18%)*	0	-	4 (4%)*	0	-
Other	7 (6%)	12 (9%)	0.7 (0.3, 1.6)	5 (4%)	5 (4%)	1.1 (0.3, 3.8)
Fatigue/lethargy	16 (14%)*	2 (2%)	9.1 (2.1, 38.5)	0	0	-
Hyperglycaemia	11 (10%)	5 (4%)	2.5 (0.9, 7.0)	5 (4%)	2 (2%)	2.8 (0.6, 14.3)
Dizziness/tinnitus/ tremor/inner ear	13 (11%)*	2 (2%)	7.4 (1.7, 31.9)	0	0	-
Ocular	9 (8%)	4 (3%)	2.5 (0.8, 8.0)	2 (2%)	1 (< 1%)	2.3 (0.2, 24.6)
Renal	4 (4%)	4 (3%)	1.1 (0.3, 4.4)	0	1 (< 1%)	0
Myopathy	5 (4%)	4 (3%)	1.4 (0.4, 5.1)	0	0	-
Thrombosis	6 (5%)	3 (2%)	2.3 (0.6, 8.8)	4 (4%)	3 (2%)	1.5 (0.3, 6.6)

CI = confidence interval; RR = relative risk; THAL = thalidomide

* Indicates statistically significant difference between treatment groups

^ Calculated during evaluation of resubmission

Source: Table 2-9, p.36 of the resubmission and RR calculated during evaluation.

Benefits/harms

6.28 A summary of the comparative benefits and harms for lenalidomide compared to BSC is presented in Table 21.

Table 21: Summary of comparative benefits and harms for lenalidomide and BSC

Benefits						
	Lenalidomide		**BSC**	**Absolute Difference**		**HR (95% CI)**
PFS: CALGB						
Progressed[a], n/N (%)	146/231 (63.2)		176/229 (76.9)	14		**0.57 (0.46, 0.71)**
Median, months (95% CI)	57.3 (44.2, 73.3)		28.9 (23.0, 36.3)	28.4		-
Progressed[b], n/N (%)	126/231 (54.5)		162/229 (70.7)	16		**0.58 (0.46, 0.73)**
Median, months (95% CI)	58.4 (42.7, 82.0)		28.9 (21.0, 35.4)	29.5		-
Progression free at 5 years, %	49.0%		32.4%	16.6%		-
OS: CALGB						
Dead[a], n/N (%)	88/231 (38.1)		120/229 (52.4)	14		**0.61 (0.46, 0.80)**
Median, months (95% CI)	113.8 (100.4, NE)		84.1 (73.8, 106.0)	29.7		-
Dead[b], n/N (%)	72/231 (31.2)		109/229 (47.6)	16		**0.57 (0.42, 0.76)**
Median, months (95% CI)	NR (NE, NE)		79.0 (70.2, 88.4)	NE		-
Alive at 5 years, %	74.4%		62.1%	12.3%		-
Harms						
	LEN	**BSC**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				LEN	**BSC**	
Neutropenia (Grade 3 or 4)						
CALGB[b]	133/224	73/221	1.80 (1.45, 2.23)	59.4	33.0	**0.26 (0.17, 0.35)**
Leukopenia (Grade 3 or 4)						
CALGB[b]	45/224	22/221	2.02 (1.26, 3.24)	20.1	10.0	**0.10 (0.04, 0.17)**
Secondary primary malignancy						
CALGB[b]	42/224	24/221	1.73 (1.08, 2.75)	18.8	10.9	**0.08 (0.01, 0.14)**

BSC = best supportive care; CI = confidence interval; HR = hazard ratio; LEN = lenalidomide; NE = not evaluable; OS = overall survival; PFS = progression free survival; RD = risk difference; RR = risk ratio

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.

Source: Table 2.5.1, p.80 and Table 2.5.3, p.85-86 of the March-2018 submission; Table 21, p100 and Table 26, p113 of the CALGB CSR. Absolute difference in % with events calculated during the evaluation.

6.29 On the basis of direct evidence presented in the pivotal CALGB trial, for every 100 patients treated with lenalidomide:

- Approximately 17 fewer patients would have progressed than if treated with BSC at 5 years after the start of treatment.
- Approximately 12 additional patients would be alive than if treated with BSC at 5 years after the start of treatment.
- Approximately 26 additional patients would have a Grade 3 or 4 neutropenic event than if treated with BSC over a median duration of treatment of 72.4 months.
- Approximately 10 additional patients would have a Grade 3 or 4 leukopenic event than if treated with BSC over a median duration of treatment of 72.4 months.
- Approximately 8 additional patients would have a secondary primary malignancy than if treated with BSC over a median duration of 72.4 months.

Clinical claim

6.30 The resubmission described lenalidomide as superior in terms of effectiveness but inferior in terms of safety compared to BSC.

6.31 The ESC considered that the transitivity issues across the trials made the results of the meta-analyses difficult to interpret, but overall, considered that the clinical claims were reasonable.

6.32 The PBAC again considered that the claim that lenalidomide had superior comparative effectiveness compared to BSC was reasonable.

6.33 The PBAC again considered that the claim that lenalidomide had inferior comparative safety compared to BSC was reasonable, noting the potential for SPMs.

6.34 The resubmission presented a revised clinical claim of non-inferior efficacy and different comparative safety relative to thalidomide. The evaluation considered this claim was supported by the clinical evidence, noting potential differences across the lenalidomide studies and thalidomide studies that impact on the capacity to make meaningful comparisons of these treatments. The PBAC previously 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 SPM (paragraph 7.14, Lenalidomide PSD, March 2018).

6.35 The ESC accepted that lenalidomide was not proven to be better than thalidomide. The large differences in PFS and OS reported in the two thalidomide versus BSC trials and the lack of statistically significant results in the meta-analyses meant ESC remained uncertain about the true comparative effectiveness between thalidomide and BSC. The results of the indirect comparisons between lenalidomide and thalidomide were difficult to interpret considering the heterogeneity and transitivity issues between the trials including different intents, durations of treatment and treatment regimens.

6.36 The PBAC considered that the claim that lenalidomide had non-inferior comparative effectiveness compared to thalidomide was reasonable.

6.37 The PBAC considered that the claim that lenalidomide had a different comparative safety profile compared to thalidomide was reasonable.

Economic analysis

6.38 The resubmission presented a stepped economic evaluation based on evidence from the RCTs and implemented a modelled cost-utility analysis for lenalidomide versus BSC.

6.39 The resubmission also presented a cost-minimisation analysis based on the indirect comparison of lenalidomide and thalidomide, as per PBAC advice (paragraphs 7.15 and 7.17, Lenalidomide PSD, March 2018).

Cost-utility analysis: lenalidomide versus BSC

6.40 The model structure and rationale are summarised in Table 22. In response to feedback from the PBAC (paragraph 7.9, Lenalidomide PSD, March 2018), the

resubmission revised the following in its approach to the CUA: reduced time horizon from 25 years to 15; incorporated the Kaplan-Meier data (from CALGB) up to the median duration follow-up (72 months) and applied extrapolated OS, PFS and time-on-treatment (ToT) data thereafter; and, applied the same pre-progression utility values to both arms.

Table 22: Summary of model structure and rationale

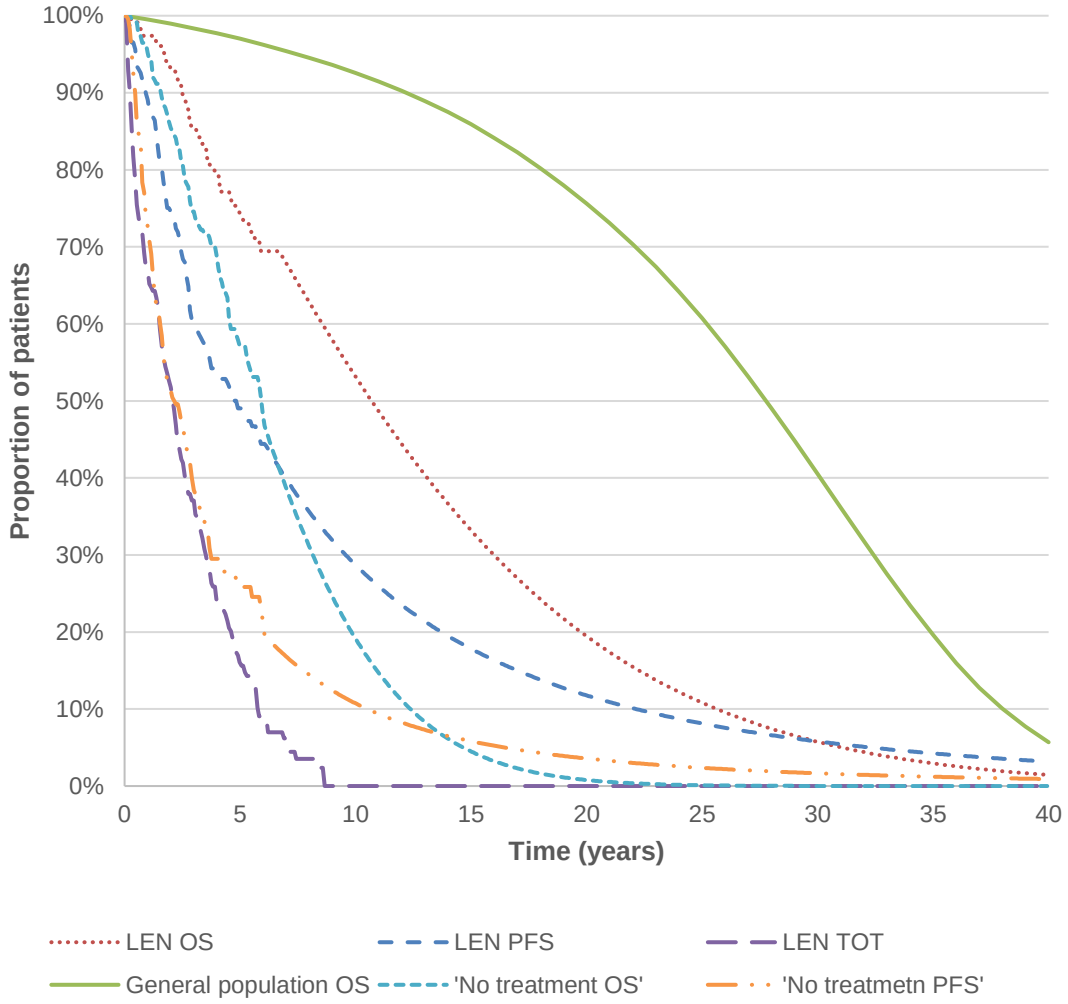
Component	Summary
Time horizon	15 years in the model base case versus 6 years in CALGB.
Outcomes	LY and QALYs gained.
Methods used to generate results	Cohort expected value, partitioned survival model.
Health states	Six model health states, comprising: pre-progression (split into 'on treatment' and 'off treatment'); post-progression (split into 'pre-second-line treatment', 'second-line treatment' and 'post second-line treatment'); death.
Cycle length	28 days.
Transition probabilities	Area under the curve analysis from CALGB using crossover adjusted OS and PFS.

LY = lifeyear; PFS = progression-free survival; QALY = quality-adjusted life year; OS = overall survival.
Source: Table 3.2, p48 of the resubmission.

6.41 The resubmission used CALGB as the basis of the efficacy estimates for lenalidomide and BSC, and ToT for lenalidomide, but IFM2005-02 to estimate the lenalidomide dose per cycle as the dose per cycle was not available for CALGB. There was therefore a mismatch between the assumed efficacy and the drug dose required to achieve it within the economic evaluation. The impact of the disjoint in the source of data on treatment exposure and treatment efficacy on cost-effectiveness was not addressed in the resubmission; however, the impact was considered to be minimal by ESC as the daily dose of lenalidomide in IFM2005-02 was [redacted] mg.

6.42 The ESC noted that in the model the fitted PFS curves exceeded OS after 30 years for lenalidomide and after 12 years for BSC (Figure 5). The ESC further questioned the plausibility of the modelled results, given the very large differences in both OS and PFS between lenalidomide and BSC. The ESC considered these issues highlighted concerns regarding the validity of the model and the resulting ICER.

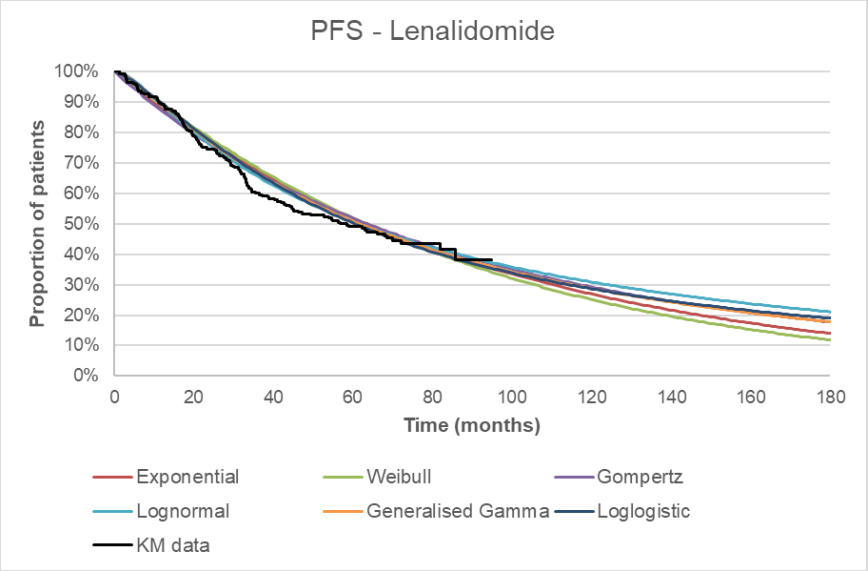
Figure 5. Comparison of long-term survival projections, lenalidomide and best supportive care



LEN = lenalidomide; OS = overall survival; PFS = progression free survival; TOT = time on treatment.
Source: Plotted on the same chart during the evaluation using 'Att 12_Section 3 cost effectiveness model v2'.

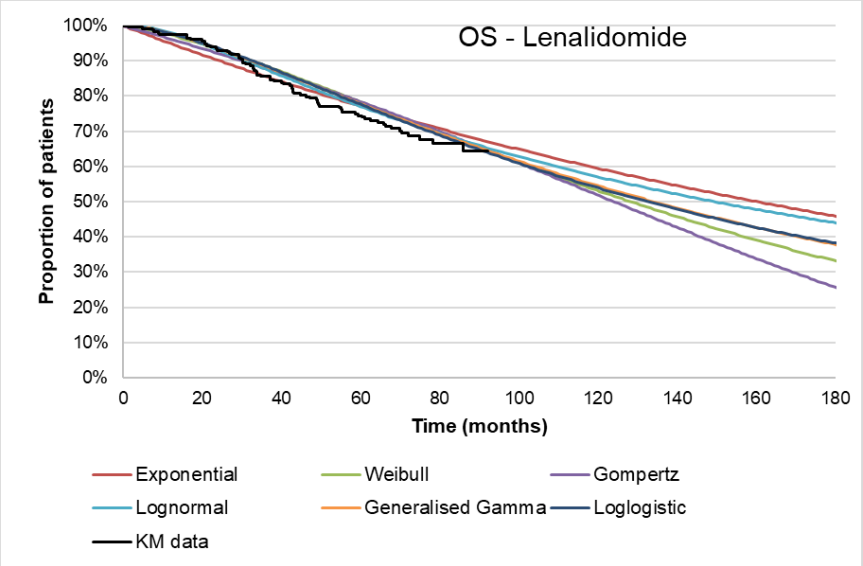
6.43 The fitted PFS and OS curves for lenalidomide are presented in Figure 6 and Figure 7, respectively. The resubmission used the generalised gamma (PFS) and Weibull (OS) curves to inform the base case of the economic model. The majority of the estimated PFS and OS gain is coming from the extrapolated period. At the start of the OS extrapolation (72 months) all of the possible extrapolation functions appear to overestimate the OS of lenalidomide relative to the Kaplan-Meier curve. For the OS extrapolations for BSC the Gompertz, generalised gamma and Weibull functions provide a more reasonable fit. The result is that the fitted curves might overestimate the OS gain for lenalidomide relative to BSC.

Figure 6. Fit of the extrapolated survival curves to the KM data for PFS with adjustment for crossover using RPSFT with adjustment for 4 covariates for CALGB dataset (lenalidomide, stratified)



KM = Kaplan-Meier; OS = overall survival; RPST = rank preserving structural failure time model.
Source: Source: Excel workbook "Section 3 CEA model_Nov 2018_v2.0", sheet "PFS", cell E50 changed to 0.

Figure 7. Fit of the extrapolated survival curves to the KM data for OS with adjustment for crossover using RPSFT with adjustment for 4 covariates for CALGB dataset (lenalidomide, stratified)



KM = Kaplan-Meier; OS = overall survival; RPST = rank preserving structural failure time model.
Source: Excel workbook "Section 3 CEA model_Nov 2018_v2.0", sheet "OS", cell E50 changed to 0.

6.44 The key drivers of the cost-utility model are presented in Table 23.

Table 23: Key drivers of the model – lenalidomide versus BSC

Description	Method/Value	Impact
Extrapolation	In the base case the treatment effect of lenalidomide was continued over the 15 year time horizon. Reducing the period over which there is a treatment effect increased the ICER.	High, favoured lenalidomide
Data source	OS, PFS and ToT in the base case were informed by the CALGB trial. Use of the pooled dataset (CALGB, IFM2005-02, GIMEMA) increased the ICER.	High, favoured lenalidomide

ICER = incremental cost-effectiveness ratio; PFS = progression-free survival; OS = overall survival; ToT = time on treatment.
Source: Table 3.31, p87 of the resubmission

6.45 The results of the stepped economic evaluation for lenalidomide versus BSC are presented in Table 24. The extension of the time horizon to 15 years (Step 2) from 6 years has a significant impact on the ICER, increasing the incremental life years gained from 0.49 to 2.24. Extension of the time horizon therefore accounts for 77% of the estimated incremental LYs gained. Applying quality of life transformations in Step 4 resulted in a base case ICER of quality-adjusted life year (QALY) - $45,000/QALY. The PBAC noted that the ICER was considerably higher than that estimated in the March 2018 submission ($15,000/QALY - $45,000/QALY).

Table 24: Results of the stepped economic evaluation – Lenalidomide vs. BSC

Step and component	Lenalidomide	BSC	Increment
Step 1: CALGB (cross-over adjusted, median follow-up 6 years) – 6-year time horizon, 1st line drug costs and outcomes			
Costs	[redacted]	[redacted]	[redacted]
LYG	4.61	4.12	0.49
Incremental cost per LYG gained			[redacted]
Step 2: CALGB data extrapolation - time horizon extended to 15 years, 1st line drug cost only			
Costs	[redacted]	[redacted]	[redacted]
LYG	7.55	5.31	2.24
Incremental cost per LYG gained			[redacted]
Step 3: CALGB data extrapolated to 15 years, incorporation of all costs (subsequent therapy, AEs)			
Costs	[redacted]	[redacted]	[redacted]
LYG	7.55	5.31	2.24
Incremental cost per LYG gained			[redacted]
Step 4: utility weights applied			
Costs	[redacted]	[redacted]	[redacted]
QALYs	5.76	4.02	1.74
Incremental cost per QALY gained (base case)			[redacted]*
March 2018 submission – Step 4			
Costs	[redacted]	[redacted]	[redacted]
QALYs	6.5	4.1	2.4
Incremental cost per QALY gained (base case)			[redacted]

AE = adverse event; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LEN = lenalidomide; LYG = life year gained; QALY = quality-adjusted life year.
* ICER calculations use published prices for bortezomib and pomalidomide
Source: Table 3.24, p.83 of the resubmission. Calculated during evaluation.

6.46 The results of selected univariate sensitivity analyses 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 spent on subsequent treatment post-progression. A sensitivity analysis using the effective prices for lenalidomide in NDMM resulted in a lower ICER.

6.47 The ESC requested a comparison of the ICERs using CALGB and the pooled efficacy dataset with and without crossover adjustment (see final row of Table 25). The ICERs ranged from the base case of $15,000/QALY - $45,000/QALY, using the CALGB efficacy data and crossover adjustment to $75,000/QALY - $105,000/QALY, using the pooled dataset with no crossover adjustment.

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

Analyses	Incremental cost	Incremental QALY	ICER
Base case	[redacted]	1.74	[redacted]
Lenalidomide effective prices for NDMM (provided by DoH)[a] 5 mg – $[redacted]; 10 mg – $[redacted]; 15 mg - $[redacted]	[redacted]	1.74	[redacted]
Time horizon (base case 15 years)			
6 years[b]	[redacted]	0.41	[redacted]
10 years		1.06	
20 years		2.13	
Efficacy source (base case OS, PFS and ToT data from CALGB)			
Pooled trial dataset (CALGB, IFM2005-02, GIMEMA)	[redacted]	0.77	[redacted]
OS extrapolation (base case Weibull)[c]			
Log-Logistic	[redacted]	1.54	[redacted]
Log-Normal		1.56	
Cross over adjustment (base case adjusted using RPSFT)[d]			
No crossover adjustment (ITT population)	[redacted]	1.34	[redacted]
Crossover adjustment censoring at crossover		1.93	
Lenalidomide treatment cost (base case applied to all 'pre-progression, on treatment' patients for full time horizon)			
Applied up-to 2.5 years (mean treatment duration in CALGB)	[redacted]	1.74	[redacted]
Time subsequent treatment (base case different cycle each line and arm)			
[redacted] cycles for each line and arm (GIMEMA)	[redacted]	1.74	[redacted]
ESC requested multivariate analysis and comparisons			
CALGB + crossover adjustment (base case)	[redacted]	1.74	[redacted]
CALGB + no crossover	[redacted]	1.34	[redacted]
Pooled dataset (CALGB, IFM2005-02, GIMEMA) + crossover adjustment	[redacted]	0.77	[redacted]
Pooled dataset (CALGB, IFM2005-02, GIMEMA) + no crossover adjustment	[redacted]	0.57	[redacted]

BSC = best supportive care; CI = confidence interval; DoH = Department of Health; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; LEN = lenalidomide; NDMM = newly diagnosed multiple myeloma; OS = overall survival; PFS = progression-free survival; RPSFTM = rank preserving structural failure time method; ToT= time on treatment.

Notes: The specific cells that were altered in the Excel spreadsheet Section 3 CEA model_Nov 2018_v2.0' were as follows: a: sheet 'Tx acquisition cost' cells [D17 to D19]; b: sheet "Model controls' cell [dropdown choice from J14]; c: sheet "Model controls' cell [dropdown choice from J115]; d: sheet "Model controls' cell [dropdown choice from J109]; e: sheet "Model controls' cell [dropdown choice from J46].

Source: Table 3.31, p87 of the resubmission. Excel spreadsheet Section 3 CEA model_Nov 2018_v2.0', sheet 'Results'.

Cost-minimisation analysis: lenalidomide versus thalidomide

6.48 The resubmission presented a cost-minimisation analysis for lenalidomide compared with thalidomide. The equi-effective doses used to inform that analysis were:

Lenalidomide 10 mg per day ≈ thalidomide 100 mg per day.

6.49 The resubmission did not use estimates of treatment exposure (dose or duration) from the clinical trials to inform the CMA.

Table 26: Results of the cost-minimisation analysis based on the recommended doses for each of the medicines

	Component	Lenalidomide			Thalidomide	
	Presentation	28 x 5 mg	28 x 10 mg	28 x 15 mg	112 x 50 mg	56 x 100 mg
A	Strength	5	10	15	50	100
B	Quantity	28	28	28	112	56
C = A x B	Pack quantity (mg)	140	280	420	5,600	5,600
D	Equi-effective daily doses					
E	Cost per mg (AEMP)	$	$ (= $ *)	$	$ (= $ / 5,600 mg)	
F = D x E	Cost per day (AEMP)	$	$	$	$	
G = C x E	Ex-manufacturer prices	$	$	$	$	

AEMP = approved ex-manufacturer price.
Source: Table 3.33, p89 of the resubmission.

6.50 The ESC noted that the assumed daily doses for lenalidomide and thalidomide were not based on any of the included trials and therefore did not take into account observed dose interruptions, dose escalations or dose reductions. However, ESC considered that the assumed equi-effective doses might be conservative as the mean dose of lenalidomide in IFM2005-02 was mg/day and the mean dose of thalidomide in MM6 was mg/day. The PBAC considered that the proposed equi-effective doses were reasonable.

6.51 The impact on the CMA of using the mean doses (no durations were available) from IFM2005-02 and MM6 was tested in a sensitivity analysis (see Table 27 below) and resulted in higher ex-manufacturer's price for lenalidomide 10 mg of $.

Table 27: Results of the cost-minimisation analysis (mean dose) based on IFM2005-02 and MM6.

	Component	Lenalidomide	Thalidomide
	Presentation	28 x 10 mg	56 x 100 mg
A	Strength	10	100
B	Quantity	28	56
C = A x B	Pack quantity (mg)	280	5,600
D	Equi-effective daily doses		
E	Cost per mg (AEMP)	$ (= $ / 1 mg)	$ (= $ / 5,600 mg)
F = D x E	Cost per day (AEMP)	$	$ (= * mg)
G = C x E	Ex-manufacturer prices	$	$

AEMP = approved ex-manufacturer price.
Source: Table 3.33, p89 of the resubmission; for thalidomide Kalf 2014 (p 3116); for lenalidomide Table 3.1, p47 of the resubmission.

6.52 The estimated ex-manufacturer price based on mg/day over months for lenalidomide and mg/day over months for thalidomide resulted in a lower price of lenalidomide per 10 mg pack of $ – see Table 28.

Table 28: Results of the cost-minimisation analysis based on mean dose and treatment duration for thalidomide

Component	Lenalidomide	Thalidomide
Strength (mg)	10 mg	100 mg
Pack quantity	28	56
Total mg/ pack	280	5,600
Max quantity packs	1 pack	1 pack
Dose (mg/day)	[redacted]	[redacted]
Treatment duration (months)	[redacted]	[redacted]
Dose duration (days)[a]	[redacted]	[redacted]
Total dose (mg)	[redacted]	[redacted]
Total packs[b]	[redacted]	[redacted]
AEMP per pack	$[redacted]	$[redacted]
Cost per course of treatment	$[redacted]	$[redacted]

AEMP = approved ex-manufacturer price.
a estimated as the product of treatment duration (months) x [redacted];
b estimated as total dose (mg) / total mg per pack.
Source: Calculated during evaluation.

6.53 The ESC noted the large differences in AEMPs when using the submission's approach of the recommended doses for each of the medicines ($[redacted]), the average trial doses ($[redacted]) and mean dose and treatment duration ($[redacted]).

6.54 The ESC noted the transitivity issues between the trials and that the fixed duration of thalidomide treatment made it difficult to estimate the treatment exposure of lenalidomide that resulted in equivalent clinical outcomes. The PBAC agreed with the ESC that given this uncertainty and the variable results in the sensitivity analyses that the cost-minimisation approach used in the resubmission based on the recommended doses for each of the medicines was reasonable (AEMP $[redacted]).

Drug cost/patient/year: $[redacted]

6.55 The resubmission proposed prices for lenalidomide 5 mg, 10 mg and 25 mg based on a weighted analysis of the prices used in the cost-utility analysis (lenalidomide versus BSC) and the prices determined from the cost-minimisation analysis (lenalidomide versus thalidomide). The weighted price in the resubmission assumed the following comparator mix: [redacted]% of patients would be treated with BSC and [redacted]% of patients would be treated with thalidomide (see Table 29). The weightings were based an

analysis of post-ASCT treatment patterns provided by the MRDR. The PBAC considered that a weighting of [redacted]% BSC and [redacted]% thalidomide would be more reasonable.

Table 29: Estimate cost per patient (lenalidomide)

	LEN 28 x 5 mg	LEN 28 x 10 mg	LEN 28 x 15 mg	Weight
CUA price versus BSC (AEMP)	[redacted]	[redacted]	[redacted]	[redacted]%
CMA price versus THAL (AEMP)	[redacted]	[redacted]	[redacted]	[redacted]%
Weighted effective price (AEMP)	[redacted]	[redacted]	[redacted]	-
Dose distribution*	22.2%	33.5%	44.3%	
Cost per patient per 28 day cycle	[redacted]			-

AEMP = approved ex-manufacturer price; BSC = best supportive care; CMA = cost-minimisation analysis; CUA = cost-utility analysis; LEN = lenalidomide; PBS = Pharmaceutical Benefits Scheme; THAL = thalidomide

* Dose distribution as used in the CUA model and based on lenalidomide in multiple myeloma PBS usage data from August 2017 to July 2018

Source: Table 3.34, p89, and Section 4.1.2.6, p99, of the resubmission

6.56 The average cost of lenalidomide per patient per 28-day cycle was estimated to be $[redacted] based on the proposed weighted effective pack prices and dose distributions. The resulting average cost of lenalidomide per patient per year was $[redacted] ($[redacted] x 365.25/28).

Estimated PBS usage & financial implications

6.57 The resubmission was considered by DUSC.

6.58 The March 2018 submission presented an epidemiological approach which assumed lenalidomide uptake for all patients who had received an ASCT. The March 2018 submission used a standard patient estimation model following the financial estimates template.

6.59 The resubmission used a dynamic individual patient level simulation of the entire MM treatment algorithm, implemented using a model in TreeAge Pro software. The lack of consistency in the simulation model was problematic in the context of producing financial estimates that could be used to inform Government deliberations and which may form the basis of subsequent risk-sharing agreements. The reliance on starting "seeds" therefore introduced a crucial element for agreement that underpins the consistency and reliability of the forward estimates. The PSCR acknowledged that the approach used in the resubmission to derive the financial estimates may have been overcomplicated and was associated with several structural and parameter uncertainties. As the reliability and validity of the simulation model presented in TreeAge could not be directly assessed by DUSC, considerations were based on a summary of the financial estimates which detailed the assumptions of the financial modelling used in the dynamic model and also the conversion of patient-months to numbers of patients.

6.60 The annual incidence rate was estimated based on Cancer Australia statistics, using 2013 data which showed an incidence of 1,637 MM patients. The resubmission estimated an annual average growth rate of [redacted]% applied to the 2013 incident patient estimate and thereafter in order to estimate incidence in the forward years of the

estimates. The derivation of the annual growth rate of [redacted]% could not be verified. DUSC noted in the previous submission, the annual growth rate for the treated population was assumed to be [redacted]% based on data derived from the Australasian Bone Marrow Transplant Recipient Registry (6.03.DUSC ADV.6, March 2018). DUSC further noted that the Global Burden of Disease Study reported that the incident growth rate for MM in the Asia Pacific region was around 5.8%[2]. For the March 2018 submission, DUSC considered that the growth rate of [redacted]% was a potential overestimate as it was high relative to the growth in the general population. DUSC commented that the annual incident growth rate was likely to be higher than [redacted]% but it was uncertain if the growth rate would be as high as that reported in the Global Burden of Disease Study.

6.61 DUSC considered that the assumptions for the proportion of patients who were symptomatic ([redacted]%) and proportion of patients' responsive to ASCT ([redacted]%) were reasonable.

6.62 The prevalence numbers used at the start of the model incorporated 500 patients receiving induction therapy consisting of bortezomib or thalidomide, or ASCT. The prevalent population for the maintenance treatment consisted of 1,100 patients at the start of the model which was split between the different treatment options of lenalidomide, thalidomide or BSC. The estimates for the prevalent population were based on what the resubmission called an "an intuitive analysis" of the 10% Medicare Australia sample data, as well as triangulation against incidence and 5-year prevalence estimates of MM from the Cancer Australia statistics website, internal sales data and expert clinical opinion. DUSC noted that the estimates of prevalent patients could not be verified from the information presented in the resubmission.

6.63 In terms of patients continuing on therapy after initiation, DUSC noted that the rate of survival for MM is slowly increasing over time.[3] DUSC further noted that the incidence of MM was also increasing. As such, DUSC considered that there was the potential for lenalidomide to be accessed by a large number of patients. It was likely that the resubmission had underestimated the size of the treated population.

6.64 The resubmission based the estimates for the uptake of lenalidomide and replaced medicines on expert opinion (survey of 44 haematologists, conducted in July-August 2018). The current scenario 'status quo' market share assumption was divided between BSC ([redacted]%) and thalidomide ([redacted]%), based on data from the MRDR, which reflected the ratios used to estimate the blended effective price. The PBAC considered that a [redacted]% BSC and [redacted]% thalidomide split would be reasonable.

6.65 The resubmission assumed that the expected prescriber behaviour after lenalidomide was listed would be [redacted]% of patients would receive lenalidomide, [redacted]% thalidomide

[2] Cowan, A.J., Allen, C., Barac, A et al. (2018) Global Burden of Multiple Myeloma :A Systematic Analysis for the Global Burden of Disease Study 2016. JAMA Oncol 4(9):1221-1227.

[3] Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no.101. Cat. no. CAN 100. Canberra: AIHW.

and [redacted]% BSC. Upon inspecting the output of the model, it appeared that lenalidomide use would start at [redacted]% in Year 1 and increase to [redacted]% in Year 6.

6.66 The assumed time on therapy with lenalidomide was [redacted] years based on a median duration of treatment of [redacted] months derived from the TreeAge model. DUSC noted that this assumption could not be verified and was longer than the median ([redacted] months) and mean ([redacted] months) duration of treatment observed in the pivotal CALGB trial. DUSC considered that for the base case, it would be appropriate to base the treatment duration on the mean time on therapy ([redacted] months) from the CALGB trial.

6.67 The resubmission assumed that treatment with lenalidomide post-ASCT will displace treatment used in the RRMM setting. While an assumption of displacement is appropriate since lenalidomide will not cure MM but will delay progression to RRMM, the resubmission estimated the change as representing a reduction in use of those other therapies. DUSC considered that the listing of lenalidomide as maintenance therapy would likely displace rather than replace existing treatment for RRMM.

6.68 During the evaluation, a disaggregated estimate of the cost offsets for thalidomide maintenance and thalidomide, lenalidomide, bortezomib, carfilzomib and pomalidomide in the RRMM setting was presented. This showed that the majority of thalidomide was replaced in the maintenance setting, there was a large decrease in the use of lenalidomide in RRMM and an increase in the use of carfilzomib. However, there was a decrease in use of carfilzomib in Year 4, which is not explained by the listing of lenalidomide. Given this, DUSC questioned the reliability of the modelling in estimating the impact of lenalidomide listing on subsequent treatment for RRMM.

6.69 The following table summarised the estimates presented in the resubmission an adjusted during evaluation.

Table 30: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Eligible patient months						
Treated patient months						
Number of patients treated[a]						
Number of packs dispensed[b]						
Estimated financial implications of lenalidomide[c]						
Cost to PBS/RPBS						
Co-payments						
Cost to PBS/RPBS less co-payments						
Estimated financial implications for replacement of thalidomide (cost savings from substituted thalidomide)[d]						
Net cost offset form substituted thalidomide						
Net cost offset attributed to displaced thalidomide (RRMM)						
Net cost offset attributed to displaced lenalidomide (RRMM)						
Net cost offset attributed to displaced bortezomib (RRMM)						
Net cost offset attributed to displaced carfilzomib (RRMM)						
Net cost offset attributed to displaced pomalidomide (RRMM)						
Total Net PBS/RPBS savings						
Net financial implications						
Net cost to PBS/RPBS[e]						

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; RRMM = relapsed and refractory multiple myeloma

Source: Table 4-5, p101, of the resubmission and Excel Workbook 'Section 4 Workbook', Sheets "3c. Impact – EFF", "4c. Displaced – EFF" and "Summary"; Excel workbook "Lenalidomide_Sec 4_DUSCTable", Sheet "Sheet 1".

[a] Revised during the evaluation. Based on the sponsor's assumptions for lenalidomide median duration of treatment of [redacted] months, based on total patient-months divided by the mean duration of treatment over 6 years (11.7 months) estimated during evaluation.

[b] Based on the assumption of [redacted] scripts per month.

[c] Based on proposed effective prices for lenalidomide.

[d] Revised during the evaluation. The estimated net cost for replaced thalidomide is based on maintenance treatment estimates from the model, the relapsed of refractory estimates were excluded during evaluation.

[e] Revised during the evaluation. The net cost presented in the resubmission did not include the co-payments associated with listing of lenalidomide and foregone co-payments due to replacement/displacement of other medicines.

6.70 The estimated net cost to the PBS/RPBS over the first six years was estimated to be $60 - $100 million.

6.71 DUSC considered that overall, the estimates presented in the submission were highly uncertain and likely to be underestimated. The main issues were:

- DUSC could not directly evaluate the financial estimates because they were developed in specialised software (TreeAge Pro) which could not be readily accessed. As acknowledged in the PSCR, the modelling approach was overly complicated and the structure and parameters informing the model could not be fully verified. DUSC considered there was a high degree of uncertainty in the utilisation estimates presented in the resubmission due to the lack of transparency

of the financial estimates model.

- The current scenario 'status quo' market share assumption was divided between BSC ([redacted]%) and thalidomide ([redacted]%). DUSC considered there was uncertainty basing these assumptions on the analysis of MRDR data presented in the submission. The utilisation of lenalidomide for maintenance therapy post ASCT was likely to be greater than estimated by the resubmission. DUSC noted that the incidence and rate of survival for MM was increasing over time. These factors were considered likely to further increase the utilisation of MM therapies beyond growth in the current treated PBS population over the forward estimates period. DUSC further considered that all new patients would commence lenalidomide and that patients on thalidomide would transition fairly rapidly so use would be greater than estimated by the resubmission.

6.72 The PBAC considered that any revised estimates would need to be presented using the standard utilisation and cost model spreadsheet and make only the following changes:

- Incorporate the revised price of lenalidomide;
- Utilise a [redacted]% BSC and [redacted]% thalidomide weighting; and
- Use the mean time on therapy ([redacted] months) from the CALGB trial.

Financial Management – Risk Sharing Arrangement

6.73 The resubmission proposed that the extension of the indication be incorporated into the existing Risk Sharing Arrangement (RSA) for lenalidomide. The resubmission did not provide details of how the existing RSA might be extended to incorporate the expansion of the indication, or to allow for potential displacement of lenalidomide in the RRMM setting

6.74 The PBAC considered that an RSA was required. The financial estimates, as acknowledged in the pre-PBAC response, are complex and the MM market is dynamic. To mitigate the uncertainty in the estimated overall increased use of lenalidomide and to address some of the DUSC concerns, the PBAC considered that a new deed should be negotiated that combines caps across the current PBS indications in NDMM and RRMM, with the maintenance post-ASCT estimates revised as recommended in paragraph 6.72 above. The PBAC recalled that the initial recommendation for RRMM was based on a sponsor proposed RSA, [redacted]. The PBAC recalled that it considered that use of lenalidomide for the treatment of RRMM [redacted]. As such, the PBAC noted that for RRMM, [redacted]; and for NDMM in patients ineligible for ASCT, [redacted]. Further, the PBAC considered that the new deed should include [redacted], i.e. any PBS expenditure beyond these caps would result in a [redacted]% rebate, rather than the current [redacted]% rebate for NDMM and RRMM.

Quality Use of Medicines

6.75 As noted for the March 2018 submission, the risk of Second Primary Malignancy (SPM) should be considered before initiating on lenalidomide (6.03.DUSC ADV.2, March 2018).

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

7 PBAC Outcome

7.1 The PBAC decided to defer the listing of lenalidomide for the maintenance treatment of patients with multiple myeloma following an autologous stem cell transplant (ASCT). The PBAC was satisfied that lenalidomide provides, for some patients, a significant improvement in efficacy over placebo, and a different toxicity profile, with notably lower rates of peripheral neuropathy, compared to thalidomide; however, the PBAC considered that at the proposed price the incremental cost-effectiveness ratio (ICER) was too high given the level of uncertainty surrounding the economic analyses, and that the estimates of overall cost were uncertain.

7.2 The PBAC acknowledged the high clinical need for effective and tolerable treatment in the maintenance setting following ASCT. This was strongly supported by the consumer comments received, noting that they described a range of benefits for lenalidomide, including improved survival and quality of life and an improved toxicity profile compared to thalidomide.

7.3 The PBAC noted that the resubmission appropriately presented a mixed comparator of thalidomide and best supportive care (BSC), as recommended at the March 2018 consideration.

7.4 The PBAC noted that the resubmission proposed relative weights for the mixed comparator of [redacted]% BSC and [redacted]% thalidomide use, based on data from the Myeloma and Related Diseases Registry (MRDR). The PBAC recalled that it had previously considered that there were limitations with the MRDR data and that the proportion of patients receiving thalidomide post-ASCT was likely to be higher than the MRDR analysis. The PBAC recalled that it has previously agreed with the DUSC that an analysis of the MRDR data by Bergin, 2017, which resulted in weightings of 53.0% BSC and 47.0% thalidomide would be more appropriate. However, at the March 2019 meeting, the PBAC, noting the pre-PBAC response, considered that post-ASCT thalidomide use was likely to be lower than that estimated in Bergin (2017) and that this was supported by a number of sources (see paragraph 5.4). The PBAC considered a more reasonable weighting would be [redacted]% BSC and [redacted]% thalidomide, which was calculated by excluding [redacted] BSC patients who were considered to be receiving active therapy from the MRDR analysis (the resubmission defined BSC as patients who were receiving no maintenance therapy or maintenance therapy other than lenalidomide or thalidomide).

7.5 The PBAC noted that the resubmission presented the same four randomised trials comparing lenalidomide to BSC as in March 2018, noting the updated results from the

Myeloma XI trial. The PBAC considered that the claim of superior efficacy and inferior safety, noting the potential for secondary primary malignancies, for lenalidomide compared to BSC were adequately supported, based primarily on the CALGB trial.

7.6 For the indirect comparison with thalidomide, the PBAC noted that the resubmission added the MM6 trial to the meta-analyses and indirect comparison of lenalidomide to thalidomide as sensitivity analyses. The PBAC considered this was reasonable, noting the large differences in progression free survival (PFS) and overall survival (OS) reported in the two thalidomide versus BSC trials (Myeloma IX and MM6) and the potential statistical errors in the analysis of MM6, which made it difficult to determine the true effectiveness of thalidomide versus BSC.

7.7 The PBAC again noted that the base case indirect comparison between lenalidomide (using the CALGB trial) and thalidomide (using the Myeloma XI trial) in post-ASCT patients resulted in a statistically significant improvement in OS for lenalidomide, but no statistically significant difference in PFS. The PBAC had previously considered this to be implausible, especially in the context of maintenance therapy where the aim of treatment is to extend the period of time in the progression free state. The PBAC noted that results of the pooled analyses indicated that the differences in PFS and OS were not statistically significant. The PBAC considered that the significant heterogeneity and transitivity issues between the lenalidomide and thalidomide trials made it difficult to determine the true comparative effectiveness between lenalidomide and thalidomide. The PBAC considered that the claims of non-inferior efficacy and different comparative safety of lenalidomide compared to thalidomide were reasonable.

7.8 The PBAC noted that the economic analysis presented in the resubmission incorporated a number of the requests made previously by the PBAC. These requests included amending the time horizon from 25 to 15 years, incorporation of Kaplan-Meier data up to the median duration of follow-up and the application of the same pre-progression utility values to both arms of the cost-utility analysis with BSC. The resubmission also appropriately presented a cost-minimisation analysis, based on the indirect comparison of lenalidomide and thalidomide.

7.9 The PBAC noted that the base case result of the stepped cost-utility analysis was $15,000/QALY - $45,000/QALY. The PBAC considered that the ICER was uncertain, noting that changes to the dataset used and removing the crossover adjustment resulted in considerable increases. The clinical plausibility of the model was also questioned given the PFS and OS arms crossed over in the extrapolation period. The PBAC considered a lenalidomide price that resulted in a base case ICER in the vicinity of that proposed in the March 2018 submission ($15,000/QALY - $45,000/QALY) would be more reasonable given these uncertainties.

7.10 Given the claim of non-inferior efficacy, the PBAC noted that the resubmission appropriately presented a cost-minimisation analysis for lenalidomide versus thalidomide. The equi-effective doses proposed in the cost-minimisation analysis were: lenalidomide 10 mg daily was equivalent to thalidomide 100 mg daily. The PBAC

recalled that although the recommended daily dose of lenalidomide was 10 mg, increasing to 15 mg after three months, it had previously considered that the dose would not be increased in the majority of patients. The PBAC noted that the equi-effective dose estimates did not consider treatment exposure (dose or duration) from the clinical trials; however, considered that due to the transitivity issues between the trials, and as the fixed duration of thalidomide treatment made it difficult to estimate the treatment exposure of lenalidomide that would result in equivalent clinical outcomes, the nominated equi-effective doses were reasonable.

7.11 The PBAC reiterated that it considered a more reasonable weighting for the mixed comparator to be [redacted]% BSC and [redacted]% thalidomide and that this should be used in future lenalidomide price calculations.

7.12 The PBAC noted that the financial implications of listing lenalidomide on the PBS/RPBS for maintenance treatment following an ASCT were high, uncertain and likely to be underestimated. The PBAC considered that any revised estimations would make only the following changes:

- Incorporate the revised price of lenalidomide;
- Utilise a [redacted]% BSC and [redacted]% thalidomide split; and
- Use the mean time on therapy ([redacted] months) from the CALGB trial.

7.13 The PBAC considered that in the context of the high and uncertain potential cost, a Risk Sharing Arrangement (RSA) would be appropriate. The PBAC considered that any RSA should also include the current lenalidomide PBS indications and include [redacted] such that any PBS expenditures beyond these caps would result in a [redacted]% rebate, as outlined in paragraph 6.74.

7.14 The PBAC advised that a minor submission would be required to address the uncertainty in the ICER and financial estimates and to provide an RSA proposal. Any revised financial estimates model must be presented in a conventional way using the standard utilisation and cost model spreadsheet for PBAC submissions.

7.15 The PBAC noted that this submission is not eligible for an Independent Review, as the submission was not rejected.

Outcome:

Deferred

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.