

6.01 LENALIDOMIDE, 5 mg, 10 mg, 15 mg, 25 mg, Capsule, Revlimid[®], Celgene Pty Ltd.

1 Purpose of Application

- 1.1 The submission requested a Section 100, Highly Specialised Drug, Authority Required, listing for lenalidomide (Revlimid[®]) in combination with bortezomib and dexamethasone (RVd) for treatment of patients with newly diagnosed multiple myeloma (NDMM) who are ineligible for an autologous stem cell transplant (ASCT). This was the first application for lenalidomide as RVd.
- 1.2 Lenalidomide in combination with dexamethasone (Rd) is currently listed on the PBS as initial therapy in patients with NDMM who are ineligible for an ASCT and for the treatment of relapsed and/or refractory multiple myeloma (RRMM), and as monotherapy for myelodysplastic syndrome.
- 1.3 The submission presented a cost utility analysis comparing RVd with Rd. In addition, the submission presented a supplementary cost utility analysis comparing RVd to a nominated secondary comparator, bortezomib in combination with melphalan and prednisolone (VMP). The key components of the clinical issue addressed by the submission are presented in Table 1.

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

| Component | Description |
|----------------|---|
| Population | Patients with newly diagnosed multiple myeloma who are ineligible for a primary stem cell transplantation. |
| Intervention | Lenalidomide in combination with bortezomib and dexamethasone (RVd): Eight 21-day cycles (24 weeks) of RVd (initial treatment), consisting of: <ul style="list-style-type: none"> • Lenalidomide 25 mg/day PO on Days 1 to 14 • Bortezomib 1.3 mg/m² IV on Days 1, 4, 8, and 11 • Dexamethasone 20 mg/day PO on Days 1, 2, 4, 5, 8, 9, 11, and 12 Continued therapy with 28-day cycles of lenalidomide in combination with dexamethasone (Rd), consisting of: <ul style="list-style-type: none"> • Lenalidomide 25 mg/day PO on Days 1-21 • Dexamethasone 40 mg/day PO on Days 1, 8, 15 and 22 |
| Comparator | Primary comparator: Rd Secondary comparator: The submission presented a supplementary economic evaluation with bortezomib in combination with melphalan and prednisolone (VMP) as the comparator. |
| Outcomes | Primary: PFS Secondary and exploratory: OS, response rate, time to response, duration of response, time to subsequent anti-myeloma therapy, safety. |
| Clinical claim | The clinical claims for RVd relative to Rd are: <ul style="list-style-type: none"> • Superior in terms of comparative efficacy • Inferior in terms of comparative safety |

IV = intravenous; OS = overall survival; PFS = progression free survival; PO = per oral
Source: Table 1-1, p.32 of the submission.

2 Requested listing

- 2.1 The details of the proposed listing for lenalidomide are summarised in Table 2.
- 2.2 Treatment consists of two phases: an initial phase of at least six 21-day cycles (recommended maximum of eight 21-cycles) of RVd, followed by a continuing phase of Rd, delivered in 28-day cycles, until disease progression.
- 2.3 The initial RVd treatment phase consists of lenalidomide 25 mg/day orally on days 1 to 14, bortezomib 1.3 mg/m² intravenously on days 1, 4, 8, and 11, and dexamethasone 20 mg/day orally on days 1, 2, 4, 5, 8, 9, 11, and 12. The Rd continuing treatment consists of lenalidomide 25 mg/day orally on days 1 to 21 and dexamethasone 40 mg/day orally on days 1, 8, 15 and 22 until disease progression.
- 2.4 To be consistent with the initial dosing of RVd in SWOG S0777, the pivotal trial, and the proposed product information, the proposed PBS indication for initial treatment with RVd would include a 14 capsule pack for a 21-day cycle, for a maximum of 24 weeks. This would require a new pack size of 14 capsules and a new PBS item number.
- 2.5 The pre-PBAC response confirmed that the proposed published and effective prices for the 14 capsule packs were as listed in Table 2 and based on the current prices of the 21 capsule packs.

Table 2: Details of the proposed listing

| Name, restriction, manner of administration and form | Max Quantity (packs) | Max Quantity (units) | Number of repeats | Dispensed Price for maximum quantity | Proprietary name and manufacturer |
|--|----------------------|----------------------|-------------------|---|-----------------------------------|
| Lenalidomide Capsule, 5 mg (initial RVd phase) | 1 | 14 | 0 | Published: \$3,415.17 Effective: \$ [REDACTED] | Revlimid® Celgene |
| Lenalidomide Capsule, 10 mg (initial RVd phase) | 1 | 14 | 0 | Published: \$3,574.11 Effective: \$ [REDACTED] | Revlimid® Celgene |
| Lenalidomide Capsule, 15 mg (initial RVd phase) | 1 | 14 | 0 | Published: \$4,168.35 Effective: \$ [REDACTED] | Revlimid® Celgene |
| Lenalidomide Capsule, 25 mg (initial RVd phase) | 1 | 14 | 0 | Published: \$4,391.66 Effective: \$ [REDACTED] | Revlimid® Celgene |
| Lenalidomide Capsule, 5 mg (continuing Rd phase) | 1 | 21 | 0 | Published: \$5,122.76 Effective: \$ [REDACTED] | Revlimid® Celgene |
| Lenalidomide Capsule, 10 mg (continuing Rd phase) | 1 | 21 | 0 | Published: \$5,361.16 Effective: \$ [REDACTED] | Revlimid® Celgene |
| Lenalidomide Capsule, 15 mg (continuing Rd phase) | 1 | 21 | 0 | Published: \$6,252.53 Effective: \$ [REDACTED] | Revlimid® Celgene |
| Lenalidomide Capsule, 25 mg (continuing Rd phase) | 1 | 21 | 0 | Published: \$6,587.49 Effective: \$ [REDACTED] | Revlimid® Celgene |

Source: Table 1-12, p.59 of the submission.

- 2.6 The proposed PBS listing criteria for lenalidomide in the initial RVd treatment phase are summarised in Table 3.

Public Summary Document – August 2019 PBAC Meeting

Table 3: Proposed PBS listing criteria – lenalidomide in initial RVD treatment phase (abridged)

| | |
|---------------------------|---|
| Category/Program: | Section 100 (Highly Specialised Drugs Program) |
| PBS indication: | Multiple Myeloma |
| Treatment phase: | Initial and Continuing |
| Restriction: | Authority required – in writing (initial treatment) and telephone (continuing treatment) |
| Clinical criteria: | <p><u>Initial treatment</u> The condition must be newly-diagnosed AND The condition must be confirmed by a histological diagnosis, AND Patient must be ineligible for a primary stem cell transplantation AND The treatment must be in combination with bortezomib and dexamethasone AND Patient must not be receiving concomitant PBS-subsidised carfilzomib, thalidomide or their analogues.</p> <p><u>Continuing treatment</u> Patient must have previously been authorized with a PBS prescription with this drug for the condition, AND Patient must not have demonstrated progressive disease, AND The treatment must be in combination with bortezomib and dexamethasone AND Patient must not be receiving concomitant PBS-subsidized carfilzomib, thalidomide or its analogues.</p> |

PBS = Pharmaceutical Benefit Scheme; RVD = lenalidomide, bortezomib and dexamethasone

Source: Table 1-13, p.61 and Table 1-14 of the submission.

- 2.7 The submission proposed that the initial phase treatment with lenalidomide (as part of RVD) be reimbursed through a new PBS listing.
- 2.8 The population proposed in the submission was patients with transplant ineligible NDMM. The pre-Sub-Committee response (PSCR) stated that the submission was for transplant ineligible patients only as the May 2018 PBAC Multiple Myeloma (MM) Stakeholder Meeting identified a greater clinical need for triplet therapy in the first-line setting in these patients. Additionally, the PBAC has historically distinguished between transplant eligible and transplant ineligible populations. The ESC noted that the May 2018 MM Stakeholder Outcome Statement stated that there was ‘less urgency’ for triplet combination therapy in NDMM transplant eligible patients, but considered that providing RVD to only transplant ineligible patients, when it might provide a benefit to those in who were transplant eligible, would likely be inequitable.
- 2.9 The ESC and PBAC noted that the aim of the key clinical trial, SWOG S0777, was to assess the efficacy of RVD in patients with NDMM without intent for immediate ASCT; however, █% of trial patients went onto receive high dose chemotherapy/ASCT or allogeneic transplant/bone marrow transplant as the first subsequent antimyeloma therapy. The ESC and PBAC considered this to be consistent with clinical practice as a patient's suitability for an ASCT can change following treatment. The PBAC noted that the trial inclusion criteria did not specifically restrict recruitment to patients considered ineligible for transplantation and considered that the PBS restriction need

not specify that the patient must be ineligible for an ASCT, especially given that the patient's eligibility can be subjective and can change following treatment.

- 2.10 The PBAC noted that although RVd is used as an induction therapy in transplant eligible patients, there is limited evidence comparing its relative efficacy to high-dose chemotherapy induction therapies in this clinical space.
- 2.11 The submission proposed that continuing phase treatment with lenalidomide (as part of Rd) beyond 24 weeks be accessed through the current continuing PBS listing for lenalidomide (as part of Rd) for NDMM patients ineligible for an ASCT. The PBAC considered this to be appropriate and noted the current lenalidomide continuing restriction would need to be amended to allow use following an initial phase of RVd treatment.
- 2.12 The submission acknowledged that a listing for RVd in NDMM would require an update of the bortezomib restriction to permit its use in combination with lenalidomide.
- 2.13 The initial (RVd) and continuing (Rd) phases of treatment will herein be referred to as overall treatment. The dosing and duration of lenalidomide in combination with bortezomib and dexamethasone matched the proposed Product Information; however, the dosing levels for dose interruption utilised in SWOG S0777 (i.e. level-1 and level-2) have not been specified in the proposed Product Information.

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

3 Background

Registration status

- 3.1 At the time of evaluation, lenalidomide was approved by the TGA for the following indications in MM:
 - in combination with dexamethasone, the treatment of patients with NDMM who are ineligible for ASCT;
 - the maintenance treatment of patients with NDMM who have undergone ASCT; and
 - in combination with dexamethasone, the treatment of MM patients whose disease has progressed after one therapy.
- 3.2 An application for lenalidomide, in combination with bortezomib and dexamethasone, for use in NDMM patients was submitted to the TGA in August 2018. The PBAC noted that in August 2019 the TGA approved registration of a new 14-day pack and the broader therapeutic indication of:

“Revlimid (lenalidomide) is indicated for the treatment of multiple myeloma”.
- 3.3 *For more detail on PBAC's view, see Section 7 PBAC outcome.*

4 Population and disease

- 4.1 Multiple myeloma is a B-cell neoplasm characterised by the multifocal, clonal proliferation of malignant plasma B cells within the bone marrow (Kumar et al., 2018; Palumbo & Anderson, 2011). The malignant proliferation of the plasma cell clone causes increasing levels of monoclonal protein (M-protein) in the serum and urine. The accumulation of M-protein may result in bone marrow failure, suppression of uninvolved immunoglobulin levels, and skeletal destruction (Munshi et al., 2012).
- 4.2 The submission noted that whilst international and Australian standard first-line treatment for NDMM includes the combined use of bortezomib and lenalidomide, current PBS restrictions for these agents preclude the use of a proteasome inhibitors (PI), such as bortezomib, in combination with an immunomodulatory agent (IMiD) such as lenalidomide. As such, most patients with transplant-ineligible NDMM in Australia are initially treated with either Rd or bortezomib in combination with cyclophosphamide and dexamethasone (VCD) (Medical Scientific Advisory Group (MSAG) of the Myeloma Foundation of Australia (MFA), 2017).
- 4.3 The submission further noted that first-line therapy in MM is an area of particular clinical importance as the quality and depth of first-line response is a prognostic factor for long-term survival (Tandon et al., 2017).

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

5 Comparator

- 5.1 The submission nominated Rd as the main comparator and VMP as a secondary comparator. The main argument provided in support of these nominations was that Rd and bortezomib-based regimens are both recommended as the preferred first-line treatments for NDMM patients who are ineligible for ASCT in Australia (MSAG of the MFA, 2017).
- 5.2 The submission nominated Rd as the primary comparator for RVd reasoning that the utilisation of lenalidomide was expected to overtake bortezomib based regimens as the mainstay of first-line therapy by 2022 and that Rd was likely to be superior to VMP based on previous PBAC decision making. It was noted that the PBAC has previously considered a multi-step pairwise indirect comparison between Rd and VMP and concluded that a more detailed evaluation of the indirect comparison was necessary, and that the results did not suggest greater survival benefits for patients treated with lenalidomide-based therapy compared to those treated with bortezomib-based therapies (Lenalidomide PSD, November 2015, paragraph 7.6).
- 5.3 The submission presented an analysis of PBS prescription data to support its future lenalidomide utilisation claim. Using relevant PBS item numbers for lenalidomide and bortezomib for NDMM transplant ineligible patients, combined with the estimated duration of treatment for each medicine, the submission estimated that ■■■% of

patients were currently receiving lenalidomide. The submission then assumed that all future patients would receive lenalidomide. The trajectory applied to the growth of lenalidomide use was not substantiated in the submission. In addition, the data for 2018 to 2019 suggested a faster rate of growth (i.e. steeper slope in the curve) for bortezomib relative to lenalidomide.

- 5.4 A survey of 44 haematologists conducted in August 2018 which was presented by the sponsor in a previous submission (Lenalidomide for maintenance therapy in NDMM post ASCT submission; March 2019) was noted during the evaluation. The haematologists reported that the majority of NDMM patients received bortezomib-based regimens compared to lenalidomide (■% vs ■% as induction prior to ASCT, ■% vs ■% as consolidation after ASCT, ■% vs ■% as maintenance after ASCT, and ■% vs ■% in transplant ineligible patients).
- 5.5 The ESC acknowledged that Rd was the preferred first-line treatment option for NDMM patients who were ineligible for ASCT. However, the ESC considered that the submission's assumption that all future patients would receive lenalidomide instead of a bortezomib-based regimen was unfounded and not adequately justified. The ESC noted the PSCR, which nominated Rd and VMP as equally weighted comparators. The ESC considered that Rd was likely to be used in 60% to 70% of NDMM patients, with a bortezomib-based regimen used in 30% to 40% of patients. The pre-PBAC response considered that this was reasonable.
- 5.6 The PBAC noted bortezomib has separate PBS listings for transplant eligible and transplant ineligible patients; however, considered the accuracy of the prescription data for each patient population was unknown and it was likely that the prescription data for transplant ineligible patients included a proportion of transplant eligible patients. The PBAC considered Rd to be the preferred first-line treatment for transplant ineligible patients, especially given the availability of carfilzomib (a PI) in the relapsed/refractory setting. However, the PBAC considered that the scenario of adding bortezomib to lenalidomide (i.e. Rd being the comparator) and the scenario of adding lenalidomide to bortezomib (i.e. VMP being the comparator) were both relevant.

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 (27) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with Rvd including delayed disease progression,

improved quality of life and reduced toxicity and side effects.

- 6.3 The PBAC noted the advice received from the Leukaemia Foundation and Myeloma Australia clarifying the likely use of RVd in clinical practice and emphasising the benefits of triplet combination therapy in the treatment of NDMM. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

- 6.4 The primary analysis presented in the submission was based on one head-to-head randomised trial (SWOG S0777) comparing RVd to Rd. SWOG S0777 comprised patients aged 18 years or older with NDMM not intended to undergo immediate ASCT as part of first-line treatment, i.e. patients who were not eligible for transplant or patients who were candidates for transplant for whom a decision had been taken to defer ASCT to a subsequent line.
- 6.5 The submission considered that the trial population was broader than the population for which PBS listing of RVd was sought and was inconsistent with Australian clinical practice, whereby all transplant-eligible patients would receive an immediate ASCT. The submission noted that this raised potential issues regarding the applicability of outcomes to the proposed PBS-eligible population as the trial population differed from the proposed PBS population.
- 6.6 The submission did not provide an indirect comparison of clinical data for RVd and VMP, despite this forming part of the economic analysis, reasoning that, based on the therapeutic relativities established by the PBAC's history of decision-making in transplant ineligible NDMM patients, lenalidomide was considered superior to bortezomib-based regimens. The ESC considered that this was not reasonable; published data were available that would have allowed an indirect comparison of RVd with VMP to be formed. The submission included an indirect comparison between Rd and VMP (as Attachment 3) but did not refer to its conduct or results and did not proceed to expand this to an indirect comparison of RVd with VMP.
- 6.7 Details of the trial presented in the submission is provided in Table 4.

Table 4: The trial presented in the submission

| Trial ID | Protocol title/ Publication title | Publication citation |
|-----------------------------|--|---------------------------------------|
| SWOG S0777 (NCT00644228) | Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. | The Lancet 2017; 389(10068), 519-527. |
| | Durie B, Hoering A, Rajkumar SV, et al. Bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (PTS) with previously untreated multiple myeloma without an intent for immediate Autologous Stem Cell Transplant (ASCT): results of the randomized phase III trial SWOG S0777. | Blood 2015; 126(23), 25. |
| | A Randomized Phase III Trial of CC-5013 (Lenalidomide, NSC-703813) and Low Dose Dexamethasone (LLD) Versus Bortezomib (PS-341, NSC-681239), Lenalidomide and Low Dose Dexamethasone (BLLD) for Induction, in Patients With Previously Untreated Multiple Myeloma Without an Intent for Immediate Autologous Stem Cell Transplant. Clinical trial registry record | Date not provided |
| | SWOG S0777 A randomized phase III trial of cc-5013 (lenalidomide, nsc-703813) and low dose dexamethasone (lld) versus bortezomib (ps-341, nsc-681239), lenalidomide and low dose dexamethasone (bld) for induction, in patients with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant. Clinical study report. | 30 January 2018 |

Source: Table 2-5, p.72-73-of the submission.

6.8 The key features of the SWOG S0777 trial are summarised in Table 5.

Table 5: Key features of the included evidence

| Trial | N | Design/duration | Risk of bias | Patient population | Outcomes | Use in modelled evaluation |
|-------------------|---------------------|---|--------------|--|--|----------------------------|
| RVd vs. Rd | | | | | | |
| SWOG S0777 | RVd: 263 Rd: 260 | Phase 3, R, OL; 05 November data cut: 50.6 months 01 December data cut: 60.6 months | Low | Patients with NDMM not intended to undergo immediate ASCT as part of first-line treatment. | PFS, OS, ORR, DOR, time to subsequent AMT, safety. | Safety, PFS and OS |

ASCT = autologous stem cell transplant; AMT = anti-myeloma therapy; DOR = duration of response; NDMM = newly diagnosed multiple myeloma; OL = open label; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; R = randomised; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib and dexamethasone.

Source: Table 2-7, p.79, Table 2-17, p.100 and Table 2-18, p.101-102 of the submission.

Comparative effectiveness

6.9 The submission presented two analyses for the treatment effect of RVd compared to Rd – the ITT analysis and a *post hoc* subgroup analysis in transplant ineligible patients (and the transplant eligible complement). The submission relied on data from the transplant ineligible subgroup, which represented approximately 50% of the total SWOG S0777 population, for the economic evaluation.

6.10 The transplant ineligible (aged > 65 or frail) and transplant eligible (aged ≤ 65 and not frail) subgroups were retrospectively defined according to conventional determinants for transplant eligibility: (i) age (> 65 years or ≤ 65 years), (ii) intent to transplant (yes or no), (iii) frailty (frail or fit/intermediate), and (iv) Eastern Cooperative Oncology

Public Summary Document – August 2019 PBAC Meeting

Group (ECOG) performance status (PS) (0 or 1 or ≥ 2). The submission justified its approach to defining the transplant ineligible and transplant eligible populations on the basis that the assessment of eligibility for ASCT was not conducted prospectively.

- 6.11 The ESC considered that age was a historical determinant for defining transplant eligibility which was no longer commonly used; instead, comorbidities and ECOG PS are currently used as the major determinants, with older patients now receiving ASCTs. In addition, the ESC considered that it was very difficult to definitively define patients as transplant eligible or ineligible as they could move from being transplant ineligible to eligible (e.g. if their renal function or ECOG PS improved), and vice versa, following treatment.
- 6.12 The ESC noted that the difficulty in attempting to retrospectively identify transplant eligibility for the purposes of assessing the cost-effectiveness of RvD in the proposed PBS listing was highlighted by █ patients (█%) classified as transplant ineligible receiving an ASCT. The PSCR acknowledged that the eligibility criteria of the SWOG S0777 trial may have resulted in the inclusion of patients that may have been eligible for transplant at some stage of their disease, but emphasised the trial was not designed to assess the evidence for RvD as an induction regimen prior to ASCT.
- 6.13 Although there is not a lot of available data, and noting that the SWOG S0777 trial was not designed to assess RvD as an induction regimen, the ESC considered that RvD may be used in the transplant eligible population as induction therapy prior to transplant, particularly in older patients without renal impairment.

ITT population

- 6.14 The results from the intention to treat (ITT) analysis from SWOG S0777 for progression free survival (PFS) and overall survival (OS) are presented in Table 6 and the corresponding Kaplan-Meier curves from the 01 December data cut-off in Figure 1 and Figure 2. The ESC noted that the results were statistically significant for both PFS and OS.

Table 6: Results of PFS and OS in the SWOG S0777 trial (ITT population, IRAC review)

| | RvD, n/N (%) | RvD, median time to event, months ^a (95% CI) | Rd, n/N (%) | Rd, median time to event, months (95% CI) | Difference in median | P value (log rank test) | Hazard ratio ^b (95% CI) |
|--|--------------------|---|--------------------|---|-------------------------|-------------------------------|---------------------------------------|
| 01 December 2016 data cut-off^c | | | | | | | |
| PFS ^d | █/263 (█%) | 42.5 (█) | █/260 (█%) | 29.9 (█) | 12.6 | 0.00862 | 0.76 (0.62, 0.93) |
| OS | 104/263 (39.5%) | 89.1 (76.1, NE) | 132/260 (50.8%) | 67.2 (58.4, 90.8) | 21.9 | 0.02786 | 0.75 (0.58, 0.97) |

CI = confidence interval; IRAC = Independent Review Adjudication Committee; ISS = international staging system; ITT = intention to treat; NE = not estimable; OS = overall survival; PFS = progression free survival; Rd = lenalidomide and dexamethasone; RvD = lenalidomide, bortezomib, and dexamethasone

^a The median is based on Kaplan-Meier estimate

^b Based on stratified Cox proportional hazards stratified by ISS stage and intent to transplant at progression comparing the hazard functions associated with treatment arms (RvD:Rd)

^c Median follow-up is 60.6 months.

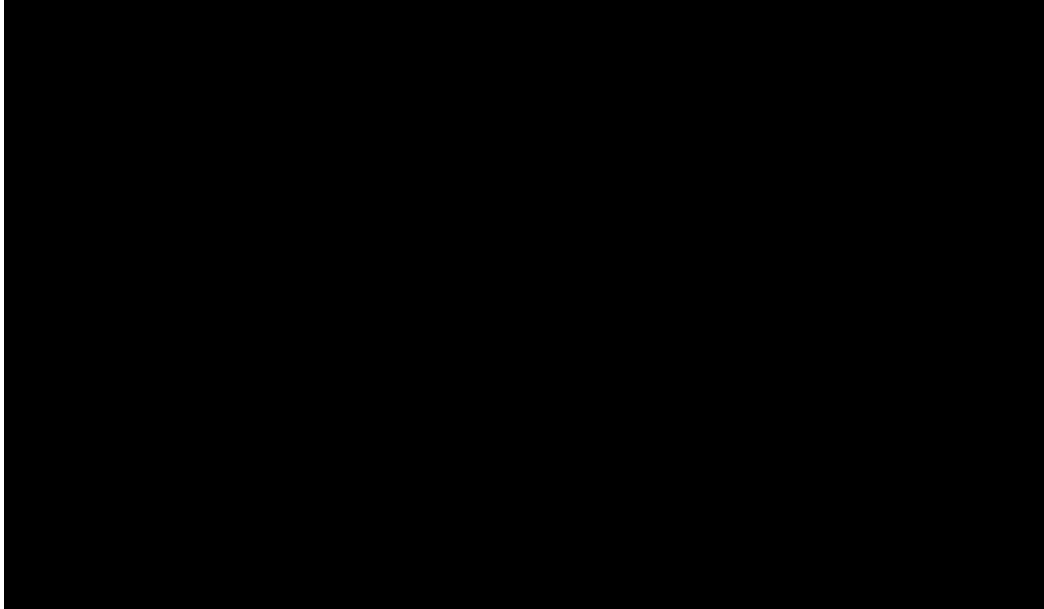
^d PFS primary analysis using SWOG censoring rule (stratified analysis)

Public Summary Document – August 2019 PBAC Meeting

Bold indicates statistically significant difference.

Source: Table 2-20, p.108, Table 2-22, p.111, of the submission.

Figure 1: Kaplan-Meier curve for PFS (01 December data cut-off, IRAC review, stratified analysis, SWOG censoring rules)

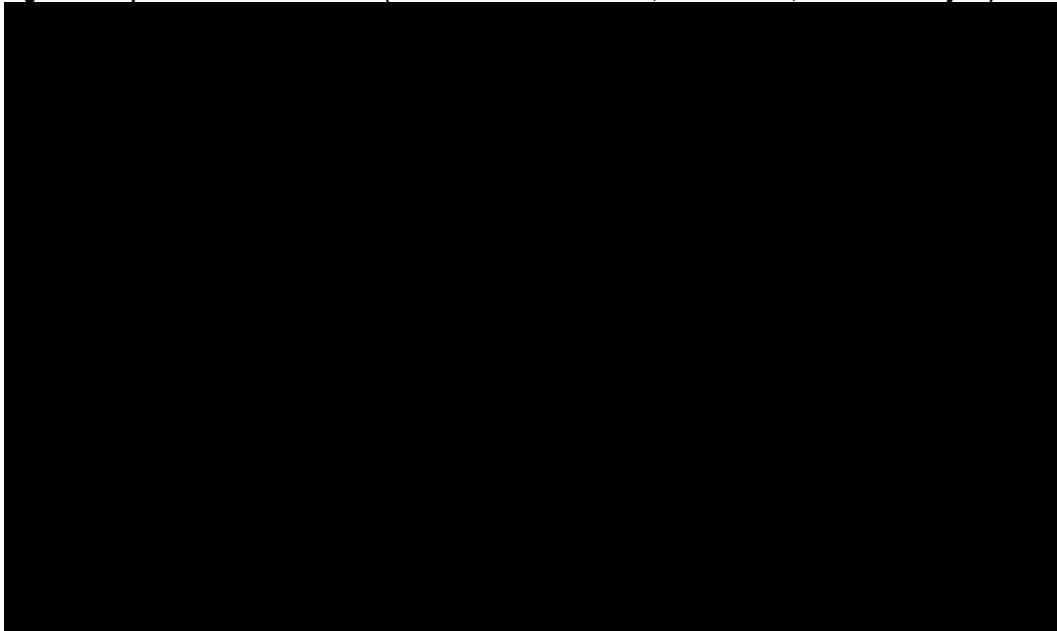


CI = confidence interval; HR = hazard ratio; IRAC = Independent Response Adjudication Committee; PFS = progression-free survival; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib and dexamethasone

Note: median follow-up is 60.6 months.

Source: Figure 2-5, p.107 of the submission.

Figure 2: Kaplan-Meier curve for OS (01 December data cut-off, IRAC review, stratified analysis)



CI = confidence interval; HR = hazard ratio; IRAC = Independent Response Adjudication Committee; OS = overall survival; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib and dexamethasone

Note: median follow-up is 60.6 months.

Public Summary Document – August 2019 PBAC Meeting

Source: Figure 2-6, p.110 of the submission.

6.15 Patients receiving RvD had a higher overall response rate than those treated with Rd (Table 7). This manifested as a higher proportion of RvD patients achieving at least a very good partial response. The submission attributed the low complete response rate in the trial to the lack of mandate to collect bone marrow needed to assess it following initial treatment (a detection bias) rather than as an absence of response. The ESC considered this to be plausible.

Table 7: Summary of myeloma response rate (01 December data cut-off, IRAC review, stratified analysis, ITT population)

| | RvD, n/N (%) | Rd, n/N (%) | OR (95% CI) | RD (95% CI) |
|---------------------------------|-----------------|-----------------|--------------------------|--------------------------|
| End of initial treatment | | | | |
| CR | 14/263 (5.3%) | 7/260 (2.7%) | | |
| VGPR | 139/263 (52.9%) | 76/260 (29.2%) | | |
| PR | 46/263 (17.5%) | 87/260 (33.5%) | | |
| SD | 12/263 (4.6%) | 35/260 (13.5%) | | |
| ORR | 199/263 (75.7%) | 170/260 (65.4%) | 1.61 (1.09, 2.39) | 0.10 (0.03, 0.18) |
| ≥ VGPR | 153/263 (58.2%) | 83/260 (31.9%) | 2.96 (2.06, 4.26) | 0.26 (0.18, 0.35) |
| Overall treatment | | | | |
| CR | /263 (%) | /260 (%) | | |
| VGPR | /263 (%) | /260 (%) | | |
| PR | /263 (%) | /260 (%) | | |
| SD | /263 (%) | /260 (%) | | |
| ORR | /263 (%) | /260 (%) | | |
| ≥ VGPR | /263 (%) | /260 (%) | | |

CI = confidence interval; CR = complete response; IRAC = Independent Response Adjudication Committee; ITT = intention to treat; OR = odds ratio; ORR = overall response rate; OS = overall survival; PR = partial response; RD = risk difference; Rd = lenalidomide and dexamethasone; RvD = lenalidomide, bortezomib and dexamethasone; SD = stable disease; VGPR = very good partial response

Note: median follow-up is 60.6 months. ORR = CR or VGPR or PR.; ≥ VGPR = CR or VGPR

Bold indicates statistically significant difference.

Source: Table 2-24, p.112 of the submission.

6.16 Patients receiving RvD had a longer median time to subsequent anti-myeloma therapy compared to those receiving Rd (Table 8).

Table 8: Time to subsequent anti-myeloma therapy (01 December data cut-off, IRAC review, ITT population)

| | RvD, n/N (%) | RvD, median time to event, months (95% CI) | Rd, n/N (%) | Rd, median time to event, months (95% CI) | Difference in median | P value (log rank test) | Hazard ratio (95% CI) ^a |
|------------------------|--------------|--|-------------|---|----------------------|-------------------------|------------------------------------|
| Time to subsequent AMT | /263 (%) | | /260 (%) | | | | |

AMT = anti-myeloma therapy; CI = confidence interval; DOR = duration of response; HR = hazard ratio; IRAC = Independent Response Adjudication Committee; ISS = international staging system; ITT = intention to treat; Rd = lenalidomide and dexamethasone; RvD = lenalidomide, bortezomib and dexamethasone

Note: median follow-up month is 60.6 months.

^aBased on stratified Cox proportional hazards model stratified by ISS stage and intent to transplant at progression.

Source: Table 2-26, p.114 of the submission.

Subgroup analyses

- 6.17 The PFS and OS results for the transplant ineligible and transplant eligible subgroups are presented in Table 9 and their Kaplan-Meier plots in Figure 3 and Figure 4.
- 6.18 The ESC noted that the PFS and OS results for the transplant ineligible and transplant ineligible subgroups were not statistically significant. This was likely due to the small sample size in the overall trial and, consequently, the subgroups. In addition, differences between the subgroups in terms of patient characteristics, such as age (median age: transplant eligible = █ years; transplant ineligible = █ years) and frailty (█% of transplant eligible were frail; █% of transplant ineligible were frail), were likely to have confounded the observed treatment effects. The submission did not present tests for interaction between the transplant eligible and transplant ineligible subgroups to support and quantify the association between the treatment effect and the covariate defining the subgroup as per the PBAC Guidelines Version 5.0, p.45 and Table 2.6.1, p.46.

Table 9: Summary of outcomes of the subgroup analysis (transplant ineligible and transplant eligible population; SWOG S0777, 01 December 2016 data cut-off, IRAC review)

| | RVd, n/N (%) | RVd median time to event, months (95% CI) | Rd, n/N (%) | Rd median time to event, months (95% CI) | Difference in median | P value (log rank test) | Hazard ratio (95% CI) |
|----------------------------------|-----------------|---|----------------|--|-------------------------|-------------------------------|--------------------------|
| Progression free survival | | | | | | | |
| Transplant ineligible | █ | █ | █ | █ | █ | █ | █ |
| Transplant eligible | █ | █ | █ | █ | █ | █ | █ |
| Overall survival | | | | | | | |
| Transplant ineligible | █ | █ | █ | █ | █ | █ | █ |
| Transplant eligible | █ | █ | █ | █ | █ | █ | █ |

CI = confidence interval; IRAC = independent response adjudication committee; NE = not estimable; OS = overall survival; PFS = progression free survival; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone

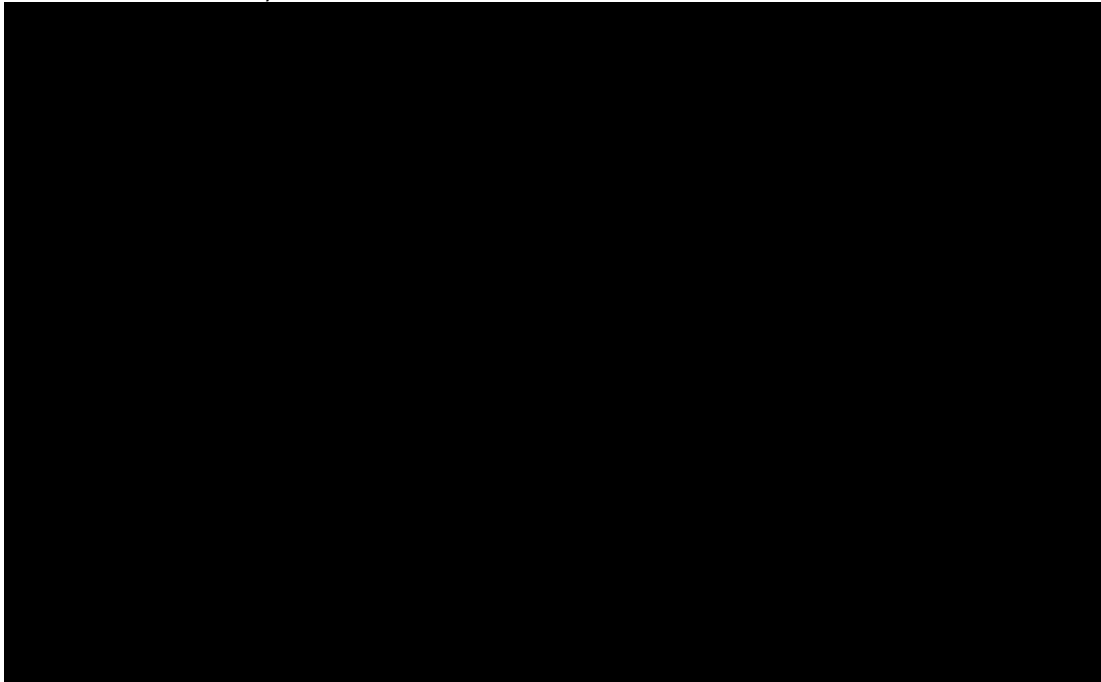
Note: PFS results presented applied EMA censoring rule.

Median follow-up is 60.6 months.

Bold indicates statistically significant difference.

Source: Table 2-38, p.136 and Table 2-39, p.139 of the submission.

Figure 3: Kaplan-Meier Estimates of PFS in the transplant ineligible and transplant eligible subgroups (SWOG S077, 01 December data cut-off)

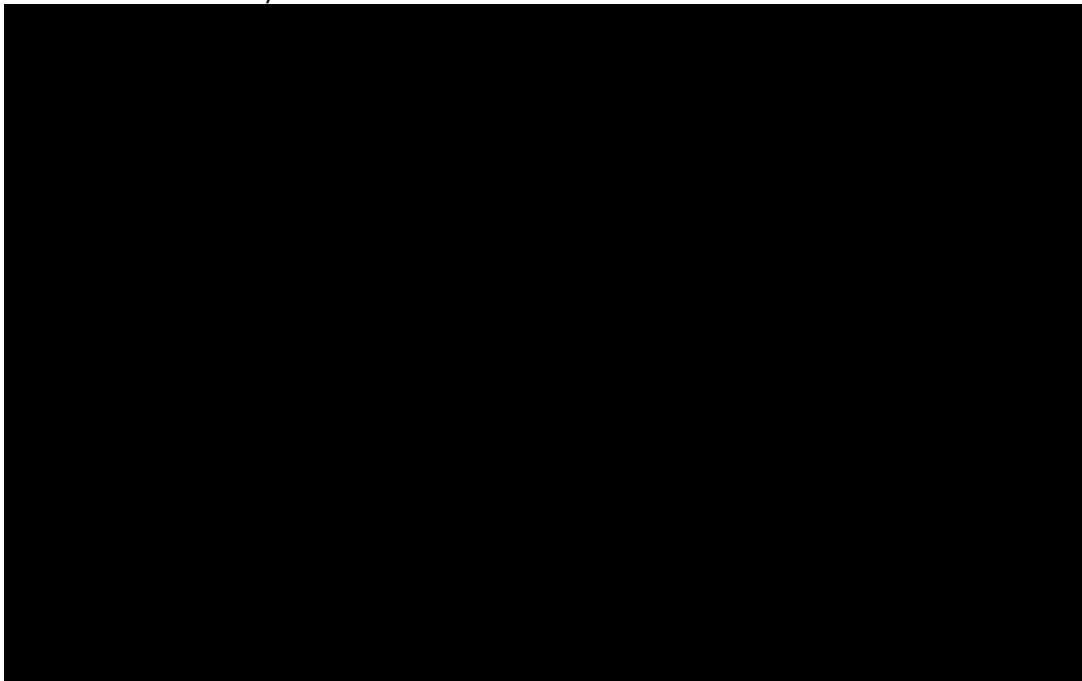


PFS = progression-free survival; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib and dexamethasone

Note: median follow-up is 60.6 months.

Source: Figure 2-8, p.137 of the submission.

Figure 4: Kaplan-Meier Estimates of OS in the transplant ineligible and transplant eligible subgroups (SWOG S0777, 01 December data cut-off)



OS = overall survival; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib and dexamethasone

Note: median follow-up is 60.6 months.

Source: Figure 2-10, p.139 of the submission.

6.19 Consistent with the ITT population, patients receiving RVd in the transplant ineligible and transplant eligible subgroups were more likely to respond to treatment compared to patients receiving Rd (Table 10). However, the difference in the overall response rate between the RVd and Rd arms in the transplant ineligible subgroup was not statistically significant. The difference for the transplant eligible subgroup was statistically significant.

Table 10: Summary of overall response rate (01 December data cut-off, IRAC review, stratified analysis)

| | RVd, n/N (%) | Rd, n/N (%) | OR (95% CI) | RD (95% CI) |
|-----------------------|--------------|-------------|-------------|-------------|
| Transplant ineligible | ██████████ | ██████████ | ██████████ | ██████████ |
| Transplant eligible | ██████████ | ██████████ | ██████████ | ██████████ |

CI = confidence interval; IRAC = Independent Response Adjudication Committee; OR = odds ratio; ORR = overall response rate; RD = risk difference; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib and dexamethasone

Note: median follow-up is 60.6 months.

ORR response rate comprises of complete response or very good partial response or partial response. RD calculated during the evaluation. Bold indicates statistically significant difference.

Source: Table 2-40, p.140 of the submission.

6.20 Quality of life data was not collected in SWOG S0777.

Indicative indirect comparison (RVd vs. VMP)

6.21 The submission did not provide an indirect treatment comparison between RVd and VMP to support its claim that RVd was superior to VMP. The PSCR stated that this comparison was not presented on the basis that:

- a head-to-head comparison was available for RVd vs Rd (SWOG S0777); and
- a multi-step indirect comparison between Rd and VMP, previously presented to the PBAC in November 2015, demonstrated that Rd resulted in at least similar progression free survival, a statistically significant improvement in overall survival and a more favourable safety profile.

6.22 Using the data provided by the submission, an indicative indirect comparison was conducted during the evaluation using the hazard ratios for RVd versus Rd and VMP versus Rd in NDMM. The results showed a statistically significant benefit of PFS and OS for RVd compared to VMP for both the transplant ineligible subgroup and ITT population of SWOG S0777 (Table 11). The PBAC has previously considered a multi-step pairwise indirect comparison of Rd versus VMP and concluded that a more detailed evaluation of the indirect comparison was necessary, as the comparison did not suggest greater survival benefits for patients treated with lenalidomide-based therapy compared to those treated with bortezomib-based therapies (paragraph 7.6, Lenalidomide PSD, November 2015).

6.23 The results for the indirect treatment comparison should be interpreted with caution as transitivity issues between the trials, including the comparability of the patient

populations (data for VMP were only available for transplant ineligible patients) and treatment conduct, for the comparison of RVd with VMP were not assessed during the evaluation.

Table 11: Indirect treatment comparison of primary outcomes (PFS and OS) for RVd and VMP

| | Treatment effect HR (95% CI) | Treatment effect P-value |
|--|---------------------------------|-----------------------------|
| Progression free survival | | |
| RVd vs. Rd; ITT population | 0.76 (0.62, 0.93) | 0.00862 |
| RVd vs. Rd, transplant ineligible subgroup | | |
| Rd vs. VMP | | |
| VMP vs. Rd | | |
| ITC: RVd vs. VMP; ITT population | | |
| ITC: RVd vs. VMP, transplant ineligible subgroup | | |
| Overall survival | | |
| RVd vs. Rd, ITT population | 0.75 (0.58, 0.97) | 0.02786 |
| RVd vs. Rd, transplant ineligible subgroup | | |
| Rd vs. VMP | | |
| VMP vs. Rd | | |
| ITC: RVd vs. VMP, ITT population | | |
| ITC: RVd vs. VMP, transplant ineligible subgroup | | |

CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; ITT = intention to treat; NE = not estimable; NR = not reported; OS = overall survival; PFS = progression free survival; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib and dexamethasone; VMP = bortezomib, melphalan and prednisolone

Note: ITC and treatment HR for VMP vs. Rd was estimated during the evaluation

Data for VMP were for the transplant ineligible population only; comparisons on an ITT basis with RVd are therefore indicative only.

Bold indicates statistically significant difference.

Source: Table 2-20, p.108, Table 2-22, p.111 and Table 3, p. 3 of Attachment 3 of the submission.

Comparative harms

- 6.24 A summary of adverse events reported in SWOG S0777 for the ITT population is presented in Table 12. Overall, treatment with RVd was associated with more treatment emergent adverse events (TEAE) than Rd. Patients were more likely to discontinue treatment with RVd compared to Rd in both the initial treatment (22.9% vs. 9.4%) and overall treatment periods (37% vs. 25%) due to TEAEs.
- 6.25 The safety profile for the transplant ineligible and transplant eligible subgroups was consistent with the ITT population; however, the frequency of TEAEs was generally higher in the transplant ineligible subgroup compared to the transplant eligible subgroup and ITT populations for both treatment periods.

Public Summary Document – August 2019 PBAC Meeting

Table 12: Summary of key adverse events in SWOG S0777 (01 December data cut-off, whole trial Safety population, ITT).

| SWOG S0777 | RVd, n/N (%) | Rd, n/N (%) | Relative risk (95% CI) | Risk difference (95% CI) |
|---|-----------------|-----------------|---------------------------|-----------------------------|
| Initial treatment phase (i.e. first 24 weeks of trial) | | | | |
| TEAE | 255/262 (97.3%) | 245/256 (95.7%) | | |
| SAE | 105/262 (40.1%) | 73/256 (28.5%) | | |
| Grade 3-4 TEAE | 200/262 (76.3%) | 176/256 (68.8%) | | |
| Grade 5 TEAE | 6/262 (2.3%) | 3/256 (1.2%) | | |
| Treatment discontinuation due to TEAE | 60/262 (22.9%) | 24/256 (9.4%) | | |
| Overall treatment | | | | |
| TEAE | 255/262 (97.3%) | 250/256 (97.7%) | | |
| SAE | 133/262 (50.8%) | 111/256 (43.4%) | | |
| Grade 3-4 TEAE | 222/262 (84.7%) | 212/256 (82.8%) | | |
| Grade 5 TEAE | 10/262 (3.8%) | 7/256 (2.7%) | | |
| Treatment discontinuation due to TEAE | 97/262 (37.0%) | 64/256 (25.0%) | | |

CI = confidence interval; ITT = intention to treat; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib and dexamethasone; SAE = serious adverse event; TEAE = treatment emergent adverse event

Note: median follow-up month is 60.6 months.

Risk difference and relative risk for transplant ineligible and transplant eligible subgroups were calculated using Review Manager 5.3.

Bold indicates statistically significant difference.

Source: Table 2-30, p.119 and Table 2-42, p. 143 of the submission; text, p.128 of the submission.

Indicative indirect comparison (RVd vs. VMP)

6.26 A naïve indirect comparison of the safety profile between RVd and VMP was conducted during the evaluation for Grade 3/4 adverse events. Based on that comparison and a naïve difference of $\geq 5\%$ as a threshold, treatment with VMP appeared to be associated with more thrombocytopenia, neutropenia, and leukopenia compared to RVd. Treatment with RVd appeared to be associated with more lymphopenia, peripheral sensory neuropathy, hypokalaemia and fatigue compared to VMP.

Benefits/harms

6.27 A summary of the comparative benefits and harms for RVd vs Rd is presented in Table 13.

Table 13: Summary of comparative benefits and harms for RVd and Rd (ITT population)

| Benefits | | | | | | |
|---|------------------|------------------|---------------------|--------------------------|------|-------------|
| | RVd | Rd | Absolute difference | HR (95% CI) | | |
| Progression free survival (median duration of follow-up 60.6 months^a) | | | | | | |
| Progressed, n/N (%) | ████/263 (████%) | ████/260 (████%) | - | 0.76 (0.62, 0.93) | | |
| Not progressed at 5 years, % (95% CI) | ████ | ████ | ████ | █ | | |
| Overall survival (median duration of follow-up 60.6 months^a) | | | | | | |
| Dead, n/N (%) | 104/263 (39.5%) | 132/260 (50.8%) | - | 0.75 (0.58, 0.97) | | |
| Alive at 5 years, % (95% CI) | ████ | ████ | ████ | █ | | |
| Harms | | | | | | |
| | RVd, n/N | Rd, n/N | RR (95% CI) | Event rate/100 patients* | | RD (95% CI) |
| | | | | RVd | Rd | |
| Initial treatment (i.e. first 24 weeks of trial) | | | | | | |
| TEAE | 255/262 | 245/256 | ████ | 97.3 | 95.7 | ████ |
| SAE | 105/262 | 73/256 | ████ | 40.1 | 28.5 | ████ |
| Grade 3/4 TEAE | 200/262 | 176/256 | ████ | 76.3 | 68.8 | ████ |
| Grade 5 TEAE | 6/262 | 3/256 | ████ | 2.3 | 1.2 | ████ |
| Treatment discontinuation due to TEAE | 60/262 | 24/256 | ████ | 22.9 | 9.4 | ████ |
| Deaths due to TEAE | 5/262 | 3/256 | ████ | 1.9 | 1.2 | ████ |
| Overall treatment | | | | | | |
| TEAE | 255/262 | 250/256 | ████ | 97.3 | 97.7 | ████ |
| SAE | 133/262 | 111/256 | ████ | 50.8 | 43.4 | ████ |
| Grade 3/4 TEAE | 222/262 | 212/256 | ████ | 84.7 | 82.8 | ████ |
| Grade 5 TEAE | 10/262 | 7/256 | ████ | 3.8 | 2.7 | ████ |
| Treatment discontinuation due to TEAE | 97/262 | 64/256 | ████ | 37.0 | 25.0 | ████ |
| Deaths due to TEAE | ████ | ████ | ████ | ████ | ████ | ████ |

CI = confidence interval; HR = hazard ratio; NR = not reported; RD = risk difference; Rd = lenalidomide and dexamethasone; RR = relative risk; RVd = lenalidomide, bortezomib and dexamethasone; SAE = serious adverse events; TEAE = treatment emergent adverse events
^a Data presented for the SWOG S0777 01 December 2016 data cut-off.
 Source: Table 2-20, p.108, Table 2-22, p.111 and Table 2-30, p.119 of the submission.

6.28 On the basis of the direct evidence presented in SWOG S0777 for every 100 patients treated with RVd rather than Rd:

- Approximately 12 fewer patients would have progressed or died at 5 years.
- Approximately 12 fewer patients would have died at 5 years.
- Approximately 7 additional patients would have serious adverse events over a median duration of treatment of 60.6 months.
- Approximately 12 additional patients would have discontinued treatment due to treatment emergent adverse events over a median duration of treatment of 60.6 months.

Clinical claim

6.29 On the basis of the direct evidence from SWOG S0777, the submission claimed that RVd was superior in terms of effectiveness and inferior in terms of safety compared to Rd. The ESC considered that the therapeutic conclusion presented in the submission

was supported by the evidence provided for the ITT population. However, the ESC considered that the evidence provided for the transplant ineligible subgroup population, which formed the basis of the economic analysis, did not adequately support the clinical claim of superior efficacy of RVd relative to Rd, as:

- the hazard ratios for PFS (HR = [REDACTED]; 95% CI: [REDACTED]) and OS (HR = [REDACTED]; 95% CI: [REDACTED]) were not statistically significant, although this was likely influenced by the small sample size; and
- the transplant ineligible subgroup was not predefined and treatment by subgroup interactions were not adequately presented.

- 6.30 The PBAC considered that the claim that RVd was superior compared to Rd in terms of effectiveness was reasonable for the ITT population of SWOG S0777.
- 6.31 The ESC considered that the safety claim of RVd relative to Rd was supported by the evidence presented for both the ITT and transplant ineligible subgroup populations. The PBAC considered that the claim of inferior comparative safety was reasonable.
- 6.32 The ESC noted that the submission did not make any clinical claim for RVd compared to VMP. However, the submission noted that in terms of comparative efficacy, RVd was likely to be superior to VMP as the PBAC previously recommended the listing of bortezomib, based on the clinical evidence that VMP was non-inferior to thalidomide in combination with melphalan and prednisolone (MPT), and the listing of Rd, on the basis that Rd was superior to MPT. Results of an indicative indirect comparison conducted during the evaluation using the data supplied by the submission suggested that superiority of RVd compared to VMP may be supported. However, the conclusions of that analysis should be interpreted with caution as they are subject to potential issues of transitivity between the studies and require further assessment.
- 6.33 The PBAC considered that RVd was likely to be superior compared to VMP in terms of comparative effectiveness, acknowledging the potential transitivity issues associated with the indirect comparison. The PBAC noted that only limited safety data, in the form of a naïve indirect comparison, were presented.

Economic analysis

- 6.34 The submission presented a stepped economic evaluation based on SWOG S0777 and implemented a modelled cost-utility analysis comparing RVd with Rd. The submission also presented a supplementary modelled economic evaluation comparing RVd with VMP. The PBAC considered that this was reasonable.
- 6.35 The model structure is summarised in Table 14.

Table 14: Summary of model structure and rationale

| Component | Summary |
|----------------------------------|---|
| Type of analysis | Cost-utility analysis comparing RVd with Rd in patients who were transplant ineligible |
| Time horizon | 20 years in the model base case versus 7 years in the key trial |
| Outcomes | PFS, OS, LYs, QALYs |
| Methods used to generate results | Partitioned survival model |
| Health states | Three health states; progression free disease, progressed disease, dead |
| Cycle length | 6 months |
| Allocation to health states | PFS and OS survival curves from the transplant ineligible subgroup in SWOG S0777 were used to distribute patients between the three model health states. Area under the curve analysis was used to estimate the time spent in each health state. The model applied Kaplan-Meier estimates up until the point where only a small number of patients remained (6 years). After this point, extrapolated data were applied. Extrapolated data was based on parametric extrapolations of the Kaplan-Meier estimates of PFS and OS. The choice of parametric function was based on the coefficient of determination (R^2) and visual inspection of the curves. |

LY = life year; OS = overall survival; PFS = progression-free survival; QALY = quality adjusted life year; Rd = lenalidomide and dexamethasone; RVD = lenalidomide, bortezomib and dexamethasone

Source: Table 3-1, p187of the submission.

6.36 Survival estimates were derived from the transplant ineligible subgroup from SWOG S0777 which was defined *post hoc*. The evaluation considered the ITT population might have formed a more appropriate basis upon which to construct the model. The PSCR stated that it was important to consider that although the relative treatment of effect of RVd versus Rd (i.e. the hazard ratios) was similar in both subgroups, the absolute treatment effect revealed that the transplant eligible subgroup performed better overall in terms of PFS and OS than the transplant ineligible population (as per Figures 3 and 4 above). Because of the differences, the sponsor considered it was appropriate to model the transplant ineligible subgroup as it was expected to best reflect survival in transplant ineligible patients. The ESC considered that the ITT population would better represent the use of RVd in Australian clinical practice. In addition, the ESC considered the *post hoc* subgroup analysis of transplant ineligible patients to be unreliable and inappropriate for the basis of the cost-effectiveness analyses as:

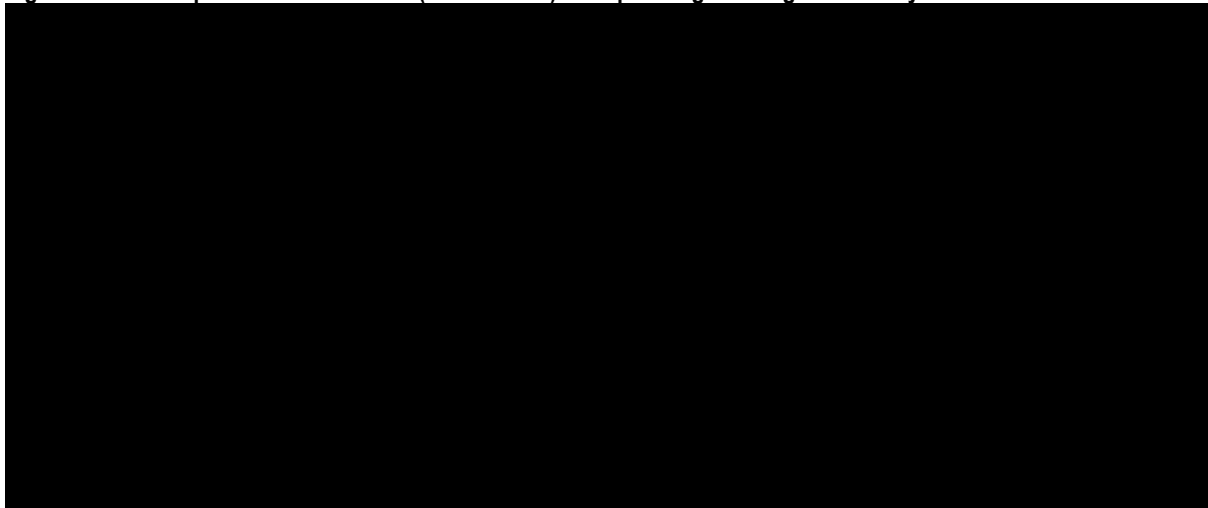
- transplant eligibility was retrospectively defined and the determinants used to define eligibility did not match those used in clinical practice, for example patients aged older than 65 years may be transplanted;
- the relative effectiveness of RVd versus Rd in terms of PFS and OS for the transplant ineligible subgroup and the transplant eligible subgroup were similar; and
- the results of the subgroup analyses were less reliable than the ITT results due to the reduced sample size.

6.37 The submission applied a time horizon of 20 years with extrapolation from 7 years of Kaplan-Meier data from SWOG S0777. The PBAC previously considered a 15-year time horizon “may be appropriate for first line myeloma therapy in this population”

(paragraph 7.15, Lenalidomide PSD, November 2015). The ESC considered that a 15 year time horizon would be appropriate.

- 6.38 Based on visual inspection and the R^2 (coefficient of determination) of the functions, the submission selected the Weibull function as the basis for extrapolation of all four survival curves (PFS and OS for RvD and Rd). The submission did not present Akaike or Bayesian information criterion statistics. No justification for this approach was provided by the submission. The ESC considered the functions selected for extrapolating the data had not been adequately justified; however, noted that using alternative functions did not substantially change the ICER.
- 6.39 The submission applied curve convergence starting at 10 years and converging at the end of the model time horizon (20 years), shown in Figure 5. When previously considering lenalidomide, the PBAC recommended the convergence of survival curves starting from Year 10 and converging by Year 12 for PFS and Year 15 for OS (paragraph 7.15, Lenalidomide PSD, November 2015). The ESC considered that PFS and OS curve convergence by Year 15 would be appropriate.

Figure 5: Model inputs: survival curves (PFS and OS) incorporating convergence at 20 years



OS = overall survival; PFS = progression free survival; Rd = lenalidomide and dexamethasone; RvD = lenalidomide, bortezomib and dexamethasone

Source: Figure 3.14, p.213 of the submission.

- 6.40 The cost of subsequent anti-myeloma therapy applied in the model was derived from the July 2019 pomalidomide PBAC submission. The submission assumed a 50% rebate to the published price of carfilzomib. The submission included a cost for treatment of neutropenia. Costs relating to other commonly experienced adverse events were not included in the economic model. The submission included administration costs associated with bortezomib. The ESC noted that bortezomib is routinely administered via subcutaneous injection and therefore, there should be no application of administration costs.

Public Summary Document – August 2019 PBAC Meeting

6.41 The submission used trial-based utility values for each of the modelled health states. These were previously accepted by the PBAC (paragraph 7.12, Lenalidomide PSD, November 2015) and were derived from EQ-5D data collected within the MM-020 trial (transplant ineligible NDMM). The ESC considered that the utility values used in the submission were appropriate and were similar to those reported by other published studies (Ramsenthaler et al., 2016 and Usmani et al., 2015).

6.42 The key drivers of the RVd versus Rd model are presented in Table 15.

Table 15: Key drivers of the model

| Description | Method/Value | Impact Base case ICER: \$ [REDACTED] /QALY |
|---|--|--|
| Applicable population | Survival estimates from transplant ineligible subgroup of SWOG S0777, rather than the ITT population | Moderate, favoured RVd ITT population: ICER = \$ [REDACTED] /QALY |
| PFS and OS curve convergence and time horizon | Convergence occurs from Year 10 to 20, rather than from Year 6 to 15. | Moderate, favoured RVd Convergence from Year 6 to 15: ICER = \$ [REDACTED] /QALY |
| Bortezomib dose exposure | Mean number of doses ([REDACTED]) in SWOG S0777 as appropriate in the base case. | High, favoured RVd 32 doses of bortezomib (maximum recommended): ICER = \$ [REDACTED] /QALY |
| Price of bortezomib and carfilzomib | 50% rebate (assumed rate) applied to price of bortezomib and carfilzomib in the submission | High |
| Relevant comparator | Rd selected as the comparator, rather than VMP | Very high, favoured RVd VMP as comparator: ICER = \$ [REDACTED] /QALY |

ICER = incremental cost-effectiveness ratio; ITT = intention to treat; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib and dexamethasone; VMP = bortezomib, melphalan and prednisolone

Source: Compiled during the evaluation

The redacted table shows ICERs in the range of \$15,000/QALY - \$75,000/QALY.

6.43 The ESC considered that the choice of comparator and its effect on the incremental costs and quality adjusted life years (QALYs) was the key driver of the model.

6.44 The results of the stepped economic evaluation for RVd versus Rd are presented in Table 16. Restricting the population to the transplant ineligible population reduced the cost per incremental life years gained from \$15,000 - \$45,000 in Step 1 to \$15,000 to \$45,000 in Step 2. This was driven by the reduction in incremental costs when going from Step 1 to Step 2, due to a reduction in lenalidomide costs. The extension of the time horizon to 20 years in Step 3, resulted in an additional 0.5577 life years compared to Step 2. However, the increase in incremental costs in the extrapolated period means that the incremental cost-effectiveness ratio (ICER) falls as the time horizon is extended.

Public Summary Document – August 2019 PBAC Meeting

Table 16: Results of the stepped economic evaluation for RVd vs Rd in transplant ineligible NDMM (50% rebate assumed to the published AEMPs of carfilzomib and bortezomib, and effective AEMPs for lenalidomide, as proposed in the submission*)

| Step and component | RVd | Rd | Increment |
|---|---------------|---------------|---------------|
| Step 1: ITT trial-based costs and outcomes | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYs | 4.2702 | 3.9405 | 0.3297 |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Step 2: transplant ineligible trial-based costs and outcomes | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYs | 3.9861 | 3.6841 | 0.3020 |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Step 3: time horizon extended to 20 years | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYs | 5.7129 | 4.8522 | 0.8577 |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Step 4: curve convergence (starting at 10 years, converging at 20 years) | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Lys | 5.6662 | 4.8552 | 0.8109 |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Step 5: utility weights applied | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALYs | 3.4528 | 2.9424 | 0.5104 |
| Incremental cost/extra QALY gained (base case) | | | \$ [REDACTED] |

AEMP = approved ex-manufacturer price; ITT = intention to treat; LY = life year; NDMM = newly diagnosed multiple myeloma; QALY = quality adjusted life year; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib and dexamethasone

* AEMPs for lenalidomide as per the submission, not the pre-PBAC updated prices presented in Table 2.

Source: Table 3-39, p234 of the submission and calculated using CUA_RVd,NDMM.xls.

The redacted table show ICERs in the range of less than \$15,000/QALY - \$45,000/QALY.

- 6.45 The results of the economic evaluation for RVd versus VMP are presented in Table 17. The model base case estimated an ICER of \$45,000/QALY - \$75,000/QALY. The difference in costs were primarily driven by lenalidomide drug costs (\$ [REDACTED]), whilst the difference in outcomes was primarily a function of superior survival (1.63 life years) assumed for RVd over VMP.
- 6.46 The submission generated survival curves comparing RVd to VMP by applying the hazard ratio for OS comparing Rd with MPT to the observed comparison of RVd with Rd (on the basis that MPT is not different to VMP and thus, the same indirect hazard ratio would apply between RVd and VMP). The submission did not present a statistical analysis to support this approach; the ICER for this comparison was therefore uncertain due to the method used to derive the comparative treatment effect. The PSCR stated that the hazard ratios used in the model for RVd relative to VMP were based on the SWOG S0777 randomised controlled trial comparing RVd and Rd and therapeutic relativities previously accepted by the PBAC. The ESC noted that the incremental QALYs gained when VMP was used as the comparator (1.03) were considerably higher than when Rd was used (0.51). The ESC considered that the

Public Summary Document – August 2019 PBAC Meeting

relative benefit of RVd compared to VMP was uncertain, given the nature of the indirect treatment comparison.

Table 17: Incremental cost effectiveness of RVd vs VMP in transplant ineligible NDMM (50% rebate assumed to the published AEMPs of carfilzomib and bortezomib and effective AEMPs for lenalidomide, as proposed in the submission*)

| Outcome | RVd | VMP | Incremental |
|---|---------------|---------------|----------------------|
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALYs | 3.45 | 2.42 | 1.03 |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |

AEMP = approved ex-manufacturer price; ICER = incremental cost-effectiveness ratio; NDMM = newly diagnosed multiple myeloma; QALY = quality adjusted life year; RVd = lenalidomide, bortezomib and dexamethasone; VMP = bortezomib, melphalan and prednisolone

* AEMPs for lenalidomide as per the submission, not the pre-PBAC updated prices presented in Table 2.

Source: Table 3.45, p 240 of the submission

The redacted table show ICERs in the range of \$45,000/QALY - \$75,000/QALY.

6.47 The key univariate sensitivity analyses conducted by the submission and additional analyses conducted during the evaluation are presented in Table 18. These results show that the model was most sensitive to the applied population, the number of bortezomib doses and the choice of comparator. During the evaluation an additional sensitivity analysis comparing RVd to VMP in the ITT population was conducted (see multivariate sensitivity analysis in Table 18). The estimated ICER was \$75,000/QALY – \$105,000/QALY compared to \$45,000/QALY – \$75,000/QALY for RVd compared to VMP in transplant ineligible NDMM.

Public Summary Document – August 2019 PBAC Meeting

Table 18: Results of sensitivity analyses (50% rebate assumed to the published AEMPs of carfilzomib and bortezomib and effective AEMPs for lenalidomide, as proposed in the submission*)

| Analyses | Incremental cost | Incremental QALY | ICER | % change from base case |
|--|------------------|------------------|---------------|-------------------------|
| Base case (Rd as comparator) | \$ [REDACTED] | 0.5104 | \$ [REDACTED] | - |
| Trial population (transplant ineligible subgroup) | | | | |
| ITT | \$ [REDACTED] | 0.6613 | \$ [REDACTED] | 16% |
| Time horizon (base case 20 years) | | | | |
| 15 years | \$ [REDACTED] | 0.4777 | \$ [REDACTED] | -3% |
| Cost of subsequent AMT (\$ [REDACTED]) | | | | |
| Increase 50% | \$ [REDACTED] | 0.5104 | \$ [REDACTED] | 10% |
| Decrease 50% | \$ [REDACTED] | 0.5104 | \$ [REDACTED] | -10% |
| Bortezomib dose exposure ([REDACTED] doses) | | | | |
| Maximum doses - 32 | \$ [REDACTED] | 0.5104 | \$ [REDACTED] | 48% |
| Estimated current PBS doses for bortezomib - 20 | \$ [REDACTED] | 0.5104 | \$ [REDACTED] | -11% |
| Curve convergence (year 10 to 20) | | | | |
| Year 10 to 15 | \$ [REDACTED] | 0.44 | \$ [REDACTED] | 8% |
| Year 6 to 15 | \$ [REDACTED] | 0.39 | \$ [REDACTED] | 19% |
| Extrapolation (Weibull) of OS and PFS | | | | |
| Gompertz | \$ [REDACTED] | 0.4663 | \$ [REDACTED] | 12% |
| Bortezomib administration fee (\$65.05/admin) | | | | |
| Zero administration fee (assume SC admin) | \$ [REDACTED] | 0.5104 | \$ [REDACTED] | -9% |
| Base case (VMP as comparator) | \$ [REDACTED] | 1.03 | \$ [REDACTED] | - |
| Multivariate | | | | |
| VMP comparator, ITT population | \$ [REDACTED] | 1.1851 | \$ [REDACTED] | 149% |

AEMP = approved ex-manufacturer price; AMT = anti-myeloma therapy; ASCT = autologous stem cell transplant; ICER = incremental cost-effectiveness ratio; ITT = intention to treat; OS = overall survival; PBS = Pharmaceutical Benefits Scheme; PFS = progression free survival; QALY = quality adjusted life year; Rd = lenalidomide and dexamethasone; RVD = lenalidomide, bortezomib and dexamethasone; SC = subcutaneous; VMP = bortezomib, melphalan and prednisolone

* AEMPs for lenalidomide as per the submission, not the pre-PBAC updated prices presented in Table 2.

Source: Table 3-47, p242, Table 3-48, p242, Table 3-49, p243, Table 3-50, p 243, Table 3-51, p243, Table 3-51, p243 of the submission. Sensitivity analyses in italics conducted by the evaluation using CUA_RVd.NDMM.xls. The specific cells altered are shown in Att. Table3.9.1.

The redacted table show ICERs in the range of \$15,000/QALY - \$105,000/QALY

6.48 The ESC noted the revised cost-utility model presented in the PSCR that:

- corrected bortezomib administration costs to \$0, reflecting subcutaneous injection costs;
- reduced the time horizon to 15 years, as per previous PBAC recommendations (however, the progression free survival and overall survival curves still converged from Year 10 to 20); and
- used a weighted comparator which consisted of 50% Rd and 50% VMP.

6.49 The ESC noted an overall weighted ICER was difficult to interpret because:

- the ICER using Rd as the comparator assessed the cost-effectiveness of adding bortezomib to Rd; whereas, the ICER using VMP as the comparator assessed the cost-effectiveness of RVD compared to a bortezomib-based regimen. Thus, the weighted ICER was not informative for assessing the cost-effectiveness of the

proposed combined lenalidomide plus bortezomib regimen against the alternate separate uses of those therapies; and

- the ICER using VMP as the comparator was highly uncertain (see paragraph 6.46) and incorporating this into a weighted ICER reduced the reliability.

6.50 The ESC considered that the economic model should:

- be based on the ITT population, as (i) RVD is likely to be used as per the broader trial population and this would better represent use of RVD in Australian clinical practice, and (ii) the use of the *post hoc* subgroup analysis was an unreliable and inappropriate basis for the cost-effectiveness analysis; and
- converge the PFS and OS curves from Year 10 to Year 15;
- have a time horizon of 15 years;
- use a bortezomib administration cost of \$0; and
- use the current effective approved ex-manufacturer prices (AEMPs) for lenalidomide 21 packs, and updated effective AEMPs for lenalidomide 14 packs.

6.51 Revised ICERs, incorporating the ESC changes, were presented in the pre-PBAC response (see Table 19).

6.52 ICERs are also presented using the net prices of carfilzomib and bortezomib as described below.



Public Summary Document – August 2019 PBAC Meeting

Table 19: Revised base case ICERs as provided in the pre-PBAC response and based on the ESC recommendations (50% rebate assumed to the published AEMP of carfilzomib and current effective AEMPs for lenalidomide as per the pre-PBAC response)*

| | ICER (\$/QALY) | | |
|----------------|---|--|--|
| | Pre-PBAC response Assumed 50% rebate for bortezomib | | |
| RVd versus Rd | \$ | | |
| RVd versus VMP | \$ | | |

AEMP = approved ex-manufacturer price; ICER = incremental cost-effectiveness ratio; ITT = intention to treat; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality adjusted life-year; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib and dexamethasone; VMP = bortezomib, melphalan and prednisolone

* Pre-PBAC model applies a 15-year time horizon, with curve convergence applied from 10 years to 15 years, and zero costs for subcutaneous administration of bortezomib. With use of the ITT population this scenario is consistent with than recommended by the ESC. Source: Table 1, p3 of the pre-PBAC response

The redacted table shows ICERs in the range of \$15,000/QALY - \$105,000/QALY.

Drug cost/patient/course

6.53 The cost per patient per course is presented in Table 20. These results show that the submission estimated a higher cost per patient per course in the economic model compared with the trial-based use of RVd and Rd. This discrepancy is due to the application of time on treatment (ToT) curves in the economic model, whereby patients can remain on treatment for the duration of the model, potentially overestimating ToT. The cost per patient per course in the financial estimates was lower than estimates derived from the economic model and trial-based use of RVd and Rd. This is a result of the application of an % compliance rate, which was not justified by the submission, and the use of PBS historical utilisation to determine the distribution of lenalidomide use across different doses representing a greater dose reduction than observed in SWOG S0777.

Table 20: Drug cost per patient for RVd and Rd

| | RVd | | | Rd | | |
|------------------------------------|-------------------------|------------------------|--|-------------------------|------------------------|--|
| | Trial dose and duration | Economic model | Financial estimates | Trial dose and duration | Economic model | Financial estimates |
| Lenalidomide mean dose reductions | % reduce dose to 15 mg | % reduce dose to 15 mg | Dose distribution based on historical PBS data; % compliance | % reduce dose to 15 mg | % reduce dose to 15 mg | Dose distribution based on historical PBS data; % compliance |
| Lenalidomide mean duration | weeks | weeks ^a | weeks | weeks | weeks ^a | weeks ^b |
| Mean number of doses of bortezomib | | | | NA | NA | NA |
| Dexamethasone dose intensity | NR | 1.0 | % compliance | NR | 1.0 | % compliance |
| Cost/patient/course ^c | \$ ^d | \$ ^e | \$ ^f | \$ ^d | \$ ^e | \$ ^f |

NA = not applicable; NR = not reported; PBS = Pharmaceutical Benefits Scheme; Rd = lenalidomide and dexamethasone; RVd =

Public Summary Document – August 2019 PBAC Meeting

lenalidomide, bortezomib and dexamethasone

^a Undiscounted mean time on treatment

^b Difference between trial mean duration and financial estimates mean duration due to rounding;

^c Includes initial and continuing treatment cycles;

^d Calculated during the evaluation using the dose reductions for lenalidomide, mean number of bortezomib doses and trial duration. Dexamethasone dose intensity assumed to be 1.0. Costs are effective prices weighted private/public

^e Undiscounted cost

^f Includes co-payment.

Source: Table 3-12, p202, Table 3-14, p205 of the submission and calculated using CUA_RVd_NDMM.xls and BIM_RVd_NDMM.xls

Estimated PBS usage & financial implications

- 6.54 The number of RVd prescriptions was based on a mean duration of treatment (■■■■ weeks) derived from the SWOG S0777 trial. The proportional use by strength was based on 2018 lenalidomide PBS utilisation data. Compliance was assumed to be ■■■%. During the evaluation it was noted that no justification was provided for the choice of the compliance rate and, it was further noted, that SWOG S0777 reported a dose reduction of ■■■% in RVd patients. DUSC considered that it was unlikely for dose intensity to be higher in the real world setting than in the trial setting. As such, DUSC considered that the mean relative dose intensity of ■■■ observed in SWOG S0777 would be more appropriate to estimate the number of RVd prescriptions in the real world setting. DUSC also noted that although dose reductions for lenalidomide were quite common, the majority of the adverse events were manageable.
- 6.55 The submission predicted the market share of RVd to be ■■■% in Year 1, increasing to ■■■% in Year 6. During the evaluation it was noted that the predicted market share after listing of RVd was based on an assumption, and no rationale for the prediction was provided by the submission. The evaluator considered that the submissions' predicted estimate of uptake of RVd may be overestimated as there was likely to be a significant proportion of patients not suitable for ASCT who will also not be suitable for RVd (PBAC, MM Stakeholder Meeting Outcome Statement, 2018). DUSC noted the response from the MM Stakeholder Meeting stating that there is a need to optimise first line treatment, with a preference for access to a combined use of a PI, such as bortezomib, and an IMiD, such as lenalidomide in the treatment of newly diagnosed multiple myeloma patients. DUSC considered that uptake would likely be higher than predicted as the majority of newly diagnosed patients will be initiated or trialed with RVd.
- 6.56 The submission included a reduction in the use of Rd and VMP if RVd was listed. The reduction was estimated as the difference in the number of patients initiating treatment of Rd and VMP without RVd listing compared with the number of patients initiating treatment if RVd was listed. The submission stated that VMP was used as a proxy for all bortezomib based regimens and that this was justified as concomitant medications taken with bortezomib were generally cheap and would generate minor financial implications. DUSC considered this approach to be reasonable.
- 6.57 The submission did not include costs to the PBS/RPBS for prophylaxis against herpes simplex virus (HSV), thromboprophylaxis or for treatment costs associated with

Public Summary Document – August 2019 PBAC Meeting

adverse events. During the evaluation this was noted to be inconsistent with the economic model presented in Section 3, which included costs of aciclovir or valaciclovir for HSV prophylaxis and G-CSF for treatment of neutropenia. It was further noted that the submission did not include changes in medicine use beyond first-line therapy. DUSC noted that use following first-line therapy was not included, and considered that RvD would likely delay the use of, rather than substitute for, later-line listings which could impact the financial estimates.

6.58 The estimated utilisation of RvD is presented in Table 21 and the estimated financial impact to the PBS/RPBS, using the prices of lenalidomide as confirmed in the pre-PBAC response and the effective price of bortezomib is in Table 22.

Table 21: Estimated use in the NDMM transplant ineligible population

| | Year 1 (2020) | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|--------------------------------|---------------|--------|--------|--------|--------|--------|
| Estimated extent of use | | | | | | |
| Patients treated with RvD | | | | | | |
| Lenalidomide 14-day packs | | | | | | |
| Lenalidomide 21-day packs | | | | | | |
| Bortezomib scripts | | | | | | |
| Dexamethasone scripts | | | | | | |

MBS = Medicare Benefits Schedule; NDMM = newly diagnosed multiple myeloma; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits; Rd = lenalidomide and dexamethasone; RvD = lenalidomide, bortezomib and dexamethasone; VMP = bortezomib, melphalan and prednisolone

Source: Table 4-14, p 259, Table 4-20, p 265, and Table 4-21, p266 of the submission and calculated using BIM_RvD_NDMM.xls; Sheet 'Celgene BI model'.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year.

Public Summary Document – August 2019 PBAC Meeting

Table 22: Estimated financial implications to lenalidomide and bortezomib with and without the availability of RVd on the PBS/RPBS (co-pay adjusted), [REDACTED] (NDMM transplant ineligible population)

| | Year 1 (2020) | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 | Total |
|---|------------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Without RVd (i.e. estimated future costs based on the current situation) | | | | | | | |
| VMP regimen | | | | | | | |
| A Bortezomib | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| B Melphalan | \$119,172 | \$111,895 | \$103,404 | \$94,004 | \$95,975 | \$97,794 | \$622,244 |
| C Prednisolone | \$8,543 | \$8,021 | \$7,413 | \$6,739 | \$6,880 | \$7,010 | \$44,606 |
| D Total (A+B+C) | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| Rd regimen | | | | | | | |
| E Lenalidomide | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| F Dexamethasone | \$144,888 | \$167,444 | \$190,325 | \$213,604 | \$226,753 | \$231,197 | \$1,174,211 |
| G Total (E+F) | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Total cost without RVd | | | | | | | |
| H VMP+Rd (D+G) | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| With RVd (i.e. potential future costs should RVd be recommended) | | | | | | | |
| VMP regimen | | | | | | | |
| I Bortezomib | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| J Melphalan | \$116,443 | \$102,494 | \$87,181 | \$70,503 | \$72,019 | \$73,383 | \$522,023 |
| K Prednisolone | \$8,347 | \$7,347 | \$6,250 | \$5,054 | \$5,163 | \$5,261 | \$37,422 |
| L Total (I+J+K) | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| Rd regimen | | | | | | | |
| M Lenalidomide | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| N Dexamethasone | \$129,132 | \$120,532 | \$110,705 | \$99,805 | \$94,321 | \$96,139 | \$650,634 |
| O Total (M+N) | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| RVd regimen | | | | | | | |
| P Lenalidomide | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| 14-day pack | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| 21-day pack | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Q Bortezomib | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| R Dexamethasone | \$21,820 | \$62,594 | \$107,971 | \$155,341 | \$176,214 | \$179,665 | \$703,605 |
| S Total (P+Q+R) | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| Total cost with RVd | | | | | | | |
| T VMP+Rd+RVd (L+O+S) | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| Total estimated change should RVd be recommended | | | | | | | |
| U With RVd - without RVd (T-H) | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| V Change in bortezomib cost (I+Q-A) | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| W Change in lenalidomide cost (M+P-E) | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |

Public Summary Document – August 2019 PBAC Meeting

PBS = Pharmaceutical Benefits Scheme; Rd = lenalidomide and dexamethasone; RPBS = Repatriation Schedule of Pharmaceutical Benefits; RVd = lenalidomide, bortezomib and dexamethasone; VMP = bortezomib, melphalan and prednisolone.

Source: Lenalidomide effective prices revised with current mark-ups and fees; [REDACTED]

The redacted table shows that at year 6, the net cost to the PBS would be \$60 - \$100 million per year.

Financial Management – Risk Sharing Arrangements

6.59 The Deed of Agreement for lenalidomide for the treatment of NDMM includes a Special Pricing Arrangement (SPA) where the effective price is achieved through a [REDACTED] by the sponsor. Additionally, the Deed also includes a Risk-Sharing Arrangement (RSA) where a [REDACTED] % is payable by the sponsor for any Commonwealth expenditure above the annual subsidisation cap.

6.60 The subsidisation cap for lenalidomide in the NDMM setting [REDACTED]. Latest utilisation data shows that lenalidomide expenditure is projected to reach approximately [REDACTED] % of the subsidisation cap of this Deed year (Year 3). The Deed term is for [REDACTED].

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

7 PBAC outcome

7.1 The PBAC recommended the listing of lenalidomide in combination with bortezomib and dexamethasone (RVd) for the treatment of patients with newly diagnosed multiple myeloma (NDMM) on the basis that it should be available only under special arrangements under Section 100 – Highly Specialised Drugs Program. The PBAC considered that the incremental use of bortezomib was cost-effective at no more than the current net price. The PBAC considered that the incremental use of lenalidomide would be cost-effective if expenditure was capped at no higher than the estimates provided in the submission, together with a price reduction to address the uncertainty in the incremental cost-effectiveness ratio (ICER) of RVd versus bortezomib in combination with melphalan and prednisolone (VMP).

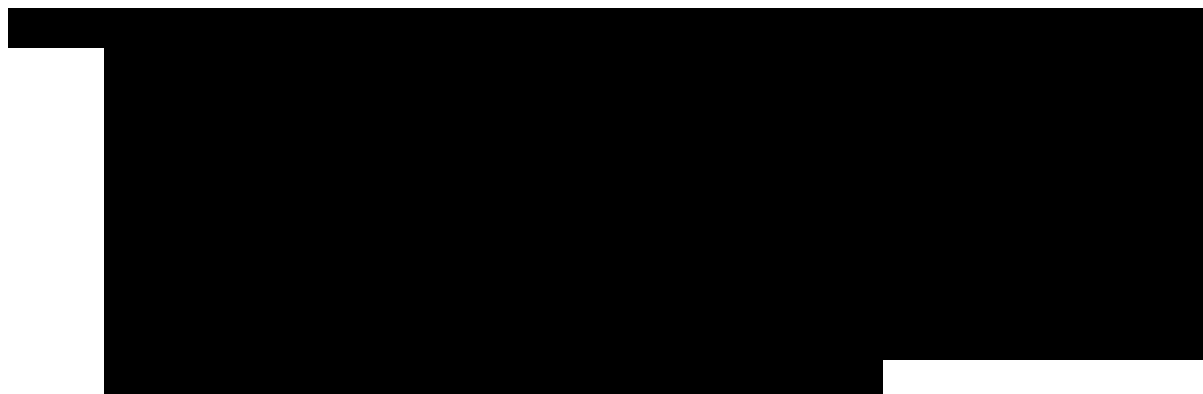
7.2 The PBAC was satisfied that RVd provides, for some patients, a significant improvement in efficacy over lenalidomide plus dexamethasone (Rd) and VMP. The PBAC acknowledged the clinical need for triplet combination therapy in the newly diagnosed patient setting, which was supported by the consumer comments, and welcomed the submission from the Sponsor in response to the Multiple Myeloma Stakeholder Meeting Outcome Statement, May 2018.

7.3 In terms of the comparator, the PBAC noted that Rd and VMP, which represented all bortezomib-based regimens, were the current first-line treatment options for patients with NDMM. The PBAC further noted that, based on PBS prescription data,

bortezomib is currently used in approximately two-thirds of NDMM patients with lenalidomide used in one-third. However, the PBAC considered that the scenario of adding bortezomib to lenalidomide (i.e. Rd being the comparator) and the scenario of adding lenalidomide to bortezomib (i.e. VMP being the comparator) were both relevant.

RVd versus Rd

- 7.4 The PBAC noted that the comparison with Rd was based on one head-to-head randomised trial (SWOG-S0777) which compared RVd to Rd in NDMM patients not intended to undergo immediate autologous stem cell transplant (ASCT) as part of first-line treatment. The PBAC noted however, that ■% of trial patients went on to receive high dose chemotherapy/ASCT or allogeneic transplant/bone marrow transplant as the first subsequent antimyeloma therapy. The PBAC agreed with the ESC that this was consistent with clinical practice as a patient's suitability for an ASCT can change following treatment.
- 7.5 The PBAC noted that the intention to treat (ITT) population analyses demonstrated that RVd was statistically significantly superior to Rd in terms of both progression free survival (PFS, HR = 0.76; 95% CI: 0.62, 0.93) and overall survival (OS, HR = 0.75; 95% CI: 0.58, 0.97). On the basis of these results, the PBAC considered that RVd was superior compared with Rd in terms of effectiveness.
- 7.6 The PBAC noted the submission presented a *post hoc* subgroup analysis of SWOG-S0777 for patients retrospectively defined as ineligible for ASCT. The PBAC agreed with ESC's concerns regarding the subgroup results as outlined in paragraph 6.36 and considered the economic analysis should be informed by the ITT results. Furthermore, the PBAC noted the treatment effect of RVd versus Rd was similar in the populations defined as transplant eligible and transplant ineligible, and considered that this supported use of RVd in the total trial population.
- 7.7 The PBAC considered that RVd was inferior compared to Rd in terms of safety, noting that RVd resulted in increased serious adverse events and treatment discontinuations.
- 7.8 The PBAC noted that the submission presented a cost-utility analysis comparing RVd to Rd based on the *post hoc* subgroup of patients who were transplant ineligible over a time horizon of 20 years.
- 7.9 The PBAC agreed with the ESC and considered that the economic model should be based on the ITT population, have a time horizon of 15 years, with convergence of the PFS and OS curves from Year 10 to 15 and remove the administration costs of bortezomib.
- 7.10 The PBAC noted that the updated base case presented in the pre-PBAC response incorporated the changes suggested by the ESC. The PBAC considered the updated economic model provided ICERs which were acceptable when the net prices for bortezomib and carfilzomib were incorporated (see Table 19).



RVd versus VMP

- 7.11 The PBAC noted that although the submission did not present a formal comparison, a multi-step pairwise indirect treatment comparison for RVd, using both the transplant ineligible subgroup and ITT population of SWOG-S0777, and VMP (data from the VISTA trial) was conducted during the evaluation process using data provided in the submission.
- 7.12 Acknowledging the multi-step nature of the comparison and the potential transitivity issues between the studies, including issues surrounding the comparability of the patient populations (data for VMP were only available for transplant ineligible patients), the PBAC considered that overall, RVd was likely to be superior to VMP in terms of PFS and OS and that the benefit of receiving RVd over VMP was likely to be greater than the benefit of adding bortezomib to Rd.
- 7.13 The PBAC noted that the submission presented a supplementary cost-utility analysis comparing RVd to VMP. The PBAC noted that the estimated survival gains in this analysis were uncertain, given that the relative benefit of RVd compared to VMP was based on the results of an indirect treatment comparison. In addition, although the PBAC considered that the benefit of receiving RVd over VMP was likely to be greater than the benefit associated with adding bortezomib to Rd treatment, the PBAC noted that the QALYs gained when VMP was the comparator (1.03) were considerably higher than when Rd was the comparator (0.51). Therefore, the PBAC considered that the ICER of \$75,000/QALY gained - \$105,000/QALY gained (Table 19), incorporating the ITT population from SWOG-S0777, a time horizon of 15 years and convergence from Years 10 to 15 was uncertain and high. The PBAC noted that the ICER was not sensitive to changes in the cost of subsequent therapies and hence, incorporating the effective price for carfilzomib in the economic model had minimal impact on the ICER.
- 7.14 The PBAC considered an ICER of approximately \$45,000/QALY gained to \$75,000/QALY gained would be acceptable for RVd versus VMP; however, advised that there could be some flexibility regarding the extent of the price reduction required, provided the financial implications for lenalidomide were capped at the estimates provided in the submission (Table 22 (row W)).

Financial implications for RVd

- 7.15 The PBAC noted the financial estimates were based on a market share for RVd of █% in Year 1 increasing to █% in Years 4 to 6. The PBAC noted that during the evaluation the uptake was considered high in comparison to the estimates provided at the 2018 MM Stakeholder meeting; however, the DUSC considered the uptake to be underestimated. The PBAC agreed with the DUSC, although noted that patients who have already commenced treatment with either lenalidomide or bortezomib (i.e. prevalent patients) should not be eligible for RVd and hence, as presented in the submission, the maximum uptake will take a number of years to be reached. The PBAC considered that the uptake proposed in the submission was appropriate for setting subsidisation caps given the uncertain ICER for the analysis comparing RVd and VMP.
- 7.16 The PBAC noted the financial estimates assumed that for the majority of patients (█% in Year 1 decreasing to █% in Years 4 to 6) RVd would replace Rd, resulting in the utilisation of bortezomib increasing with the listing of RVd. For the remaining patients, RVd would replace VMP, resulting in the utilisation of lenalidomide increasing. The PBAC noted the substitution of Rd primarily was as a result of the assumed increase in use of Rd (and corresponding decrease in use of VMP) over time in the absence of RVd, as well as greater substitution of Rd relative to VMP. The PBAC considered the increased use of Rd over time was uncertain and possibly overestimated, and the greater substitution of Rd relative to VMP to be poorly supported. This resulted in the estimated increase in utilisation of bortezomib to be likely overestimated and the estimated increase in utilisation of lenalidomide to be likely underestimated. The PBAC considered that, in the absence of reliable data to inform the future patterns of substitution, it would have been more appropriate to assume the substitution of Rd and VMP would be proportional to the market share (e.g. in Years 4 to 6, █% of replacement would be from Rd with █% from VMP).
- 7.17 The PBAC considered that the incremental expenditure of lenalidomide should be capped at no higher than the estimates presented in Table 22 (row W). The PBAC noted that utilisation has been tracking at approximately █ of the current subsidisation caps for lenalidomide in NDMM. The PBAC advised that these caps would need to be revised based on current PBS utilisation in order to cap the additional use in NDMM associated with combination therapy, noting that the estimates for lenalidomide in the Rd regimen provided in the submission (Table 22, row E) appeared to be overestimated compared to the data available on current use. The PBAC also considered that the rebate payable above the subsidisation caps would need to █%.
- 7.18 The PBAC reiterated from the March 2019 and July 2019 meetings that its preference was for a single Risk Sharing Arrangement (RSA) that incorporated all lenalidomide PBS listings in a single expenditure cap, beyond which rebates would apply. The PBAC also noted that the TGA registered indication for lenalidomide had been simplified to

‘the treatment of multiple myeloma’ and would welcome an application for a similarly simplified PBS listing.

RVd restriction

- 7.19 The PBAC considered, given the similar treatment effect in patients defined as transplant eligible and transplant ineligible in SWOG S0777, that the population eligible for PBS treatment should be consistent with the full trial population. The PBAC noted that the trial was in patients not intending to undergo immediate ASCT, although as expected in clinical practice, some patients did subsequently undergo ASCT. Therefore, consistent with the trial, the PBAC considered that the restriction for lenalidomide need not specify that a patient must be ineligible for a stem cell transplant.
- 7.20 The PBAC noted the arguments in the pre-PBAC response regarding restricting RVd to transplant ineligible patients, including that SWOG S0777 was not designed to assess RVd as an induction regimen. However, the PBAC considered removing the criteria regarding being transplant ineligible from the restriction would not lead to inappropriate use of RVd. The PBAC also noted that in the pre-PBAC response the sponsor stated that they were willing to provide estimates of the financial impact of listing RVd for a population which was broader than the transplant ineligible population. However, the PBAC considered the additional use would likely be relatively small noting that based on PBS prescription data the minority of NDMM patients are classified transplant eligible, and that the incremental use in patients undergoing a transplant would be limited to the cycles prior to transplant as the use following the transplant is covered by the recommendation from the July 2019 meeting to list lenalidomide for maintenance treatment post ASCT. Noting the uncertain incremental efficacy and cost-effectiveness for RVd versus VMP, the PBAC reiterated that the incremental PBS expenditure for lenalidomide should not exceed that presented in Table 22 (row W) despite the recommended revision to the restriction.
- 7.21 The PBAC noted that prevalent patients currently receiving Rd or bortezomib-based regimens should not be allowed to switch to RVd as there was no available evidence for this sequencing.
- 7.22 The PBAC noted that the current continuing restriction for lenalidomide, as Rd, in NDMM patients ineligible for an ASCT would have to be updated to allow Rd use to continue following the initial RVd phase. The current initial and continuing PBS-subsidised treatment restrictions for bortezomib in NDMM patients would also have to be updated to allow use in combination with lenalidomide.
- 7.23 The PBAC considered that Authority Required (written) was appropriate for initial supply and Authority Required (telephone) was appropriate for continuing supply.

Public Summary Document – August 2019 PBAC Meeting

- 7.24 Lenalidomide is not suitable for prescribing by nurse practitioners as antineoplastic agents are currently considered to be out of scope for prescribing by nurse practitioners.
- 7.25 The PBAC considered the Early Supply Rule should not apply to lenalidomide.
- 7.26 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for lenalidomide:
- (a) The treatment was expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies, noting the PBAC considered RVd to be superior in terms of efficacy compared to Rd;
 - (b) The treatment is not expected to address a high and urgent unmet clinical need because there are alternative therapies (Rd and bortezomib-based regimens) available;
 - (c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.27 The PBAC recommended that lenalidomide should not be treated as interchangeable on an individual patient basis with any other drugs.

Outcome:

Recommended

8 Recommended listing

Amend existing/recommended listing as follows:

| Name, restriction, manner of administration and form | Max Quantity (packs) | Max Quantity (units) | Number of repeats | Proprietary name and manufacturer |
|---|-----------------------------|-----------------------------|--------------------------|--|
| Lenalidomide Capsule, 5 mg (initial RVd phase) | 1 | 14 | 0 | Revlimid® Celgene |
| Lenalidomide Capsule, 10 mg (initial RVd phase) | 1 | 14 | 0 | Revlimid® Celgene |
| Lenalidomide Capsule, 15 mg (initial RVd phase) | 1 | 14 | 0 | Revlimid® Celgene |
| Lenalidomide Capsule, 25 mg (initial RVd phase) | 1 | 14 | 0 | Revlimid® Celgene |
| Lenalidomide Capsule, 5 mg (continuing Rd phase) | 1 | 21 | 0 | Revlimid® Celgene |
| Lenalidomide Capsule, 10 mg (continuing Rd phase) | 1 | 21 | 0 | Revlimid® Celgene |
| Lenalidomide Capsule, 15 mg (continuing Rd phase) | 1 | 21 | 0 | Revlimid® Celgene |
| Lenalidomide Capsule, 25 mg (continuing Rd phase) | 1 | 21 | 0 | Revlimid® Celgene |

Public Summary Document – August 2019 PBAC Meeting

| | |
|--------------------------|--|
| Category/Program | Section 100 (Highly Specialised Drugs Program) |
| Condition | Multiple Myeloma |
| Prescriber type | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| PBS Indication | Newly-diagnosed multiple myeloma |
| Treatment phase | Initial treatment |
| Restriction | <input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required – Electronic <input type="checkbox"/> Streamlined |
| Clinical criteria | <p>The condition must be newly-diagnosed AND The condition must be confirmed by a histological diagnosis, AND Patient must be ineligible for a primary stem cell transplantation AND The treatment must be in combination with bortezomib and dexamethasone AND Patient must not be receiving concomitant PBS-subsidised carfilzomib, thalidomide or their analogues, AND <i>Patient must not have previously been treated with lenalidomide or bortezomib for this condition</i> AND <i>Patient must not receive more than 8 cycles of treatment with lenalidomide in combination with bortezomib and dexamethasone.</i></p> <p>The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed Multiple Myeloma lenalidomide Authority Application – Supporting Information Form, which includes details of the histological diagnosis of multiple myeloma, and ineligibility for prior stem cell transplant; and nomination of which disease activity parameters will be used to assess response; and (3) a signed patient acknowledgement.</p> <p>To enable confirmation of eligibility for treatment, current diagnostic reports of at least one of the following must be provided:</p> <ul style="list-style-type: none"> (a) the level of serum monoclonal protein; or (b) Bence-Jones proteinuria – the results of 24-hour urinary light chain M protein excretion; or (c) the serum level of free kappa and lambda light chains; or (d) bone marrow aspirate or trephine; or (e) if present, the size and location of lytic bone lesions (not including compression fractures); or (f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or (g) if present, the level of hypercalcaemia, corrected for albumin concentration. <p>As these parameters will be used to determine response, results for either (a) or (b) or (c) should be provided for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) should be provided. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be provided.</p> |

Public Summary Document – August 2019 PBAC Meeting

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| Note | <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9862 HOBART TAS 7001</p> |
| Notes | Patients receiving this drug under the PBS listing must be registered in the i-access risk management program. |
| Note | <i>Special Pricing Arrangements apply.</i> |
| Caution | <i>This drug is a category X drug and must not be given to pregnant women. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans cannot be ruled out.</i> |

| | |
|--------------------------|---|
| Category/Program | Section 100 (Highly Specialised Drugs Program) |
| Condition | Multiple Myeloma |
| Prescriber type | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| PBS Indication | Newly-diagnosed multiple myeloma |
| Treatment phase | Continuing treatment |
| Restriction | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined |
| Clinical criteria | <p>Patient must have previously been authorised with a received PBS subsidised treatment with this drug for the condition, AND Patient must not have demonstrated progressive disease, AND The treatment must be in combination with bortezomib and dexamethasone AND Patient must not be receiving concomitant PBS-subsidised carfilzomib, thalidomide or its analogues, AND Patient must not receive more than 7-8 cycles of treatment with lenalidomide in combination with bortezomib and dexamethasone under this restriction.</p> |

Public Summary Document – August 2019 PBAC Meeting

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| Definitions | <p>Progressive disease is defined as at least 1 of the following:</p> <p>(a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or</p> <p>(b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or</p> <p>(c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or</p> <p>(d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or</p> <p>(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or</p> <p>(f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or</p> <p>(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).</p> <p>Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.</p> |
| Note | <p><i>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i></p> <p><i>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</i></p> <p><i>Applications for authority to prescribe should be forwarded to:</i> <i>Department of Human Services</i> <i>Complex Drugs</i> <i>Reply Paid 9862</i> <i>HOBART TAS 7001</i></p> |
| Notes | Patients receiving this drug under the PBS listing must be registered in the i-access risk management program. |
| Note | <i>Special Pricing Arrangements apply.</i> |
| Caution | <i>This drug is a category X drug and must not be given to pregnant women. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans cannot be ruled out.</i> |

The flow-on changes to the current lenalidomide continuing restriction for use in NDMM patients who are ineligible for ASCT to allow treatment with Rd following induction with RVd are presented below (PBS codes: 11042E and 11062F).

| | |
|--------------------------|--|
| Category/Program | Section 100 (Highly Specialised Drugs Program) |
| Condition | Multiple Myeloma |
| Prescriber type | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| PBS Indication | Newly-diagnosed multiple myeloma |
| Treatment phase | Continuing treatment |
| Restriction | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required – Electronic <input type="checkbox"/> Streamlined |
| Clinical criteria | Patient must have previously been authorised with a PBS prescription for <i>lenalidomide in combination with dexamethasone</i> this drug for this condition , OR |

Public Summary Document – August 2019 PBAC Meeting

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| | <p><i>Patient must have previously been authorised with a PBS prescription for lenalidomide in combination with bortezomib and dexamethasone for a maximum of 8 cycles,</i> AND Patient must not be demonstrated progressive disease, AND Patient must not be receiving concomitant PBS-subsidised bortezomib, thalidomide or its analogues, AND The treatment must be in combination with dexamethasone.</p> |
| Definitions | <p>Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause). Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.</p> |
| Note | <p>Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday)</p> |
| Note | <p>Patients receiving this drug under the PBS listing must be registered in the i-access risk management program.</p> |
| Note | <p>Special Pricing Arrangements apply.</p> |
| Caution | <p>This drug is a category X drug and must not be given to pregnant women. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans cannot be ruled out.</p> |

The flow-on changes to the current initial and continuing bortezomib restrictions for use in NDMM patients are presented below (PBS codes: 4403R, 7238Y, 4429D and 7274W).

Authority code: 7963

| | |
|--------------------------|--|
| Category/Program | Section 100 (Efficient funding of chemotherapy) |
| Condition | Multiple Myeloma |
| Prescriber type | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| PBS Indication | Symptomatic multiple myeloma |
| Treatment phase | Initial PBS-subsidised treatment |
| Restriction | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required – Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria | <p>The condition must be newly-diagnosed AND Patient must be ineligible for high dose chemotherapy,</p> |

Public Summary Document – August 2019 PBAC Meeting

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| | <p>AND Patient must not be receiving concomitant PBS-subsidised thalidomide or its analogues, AND The treatment must be in combination with a corticosteroid and melphalan or cyclophosphamide, <i>OR</i> <i>The treatment must be in combination with lenalidomide and dexamethasone,</i> AND Patient must not receive more than 4 cycles of treatment with bortezomib under this restriction.</p> |
| Note | Special Pricing Arrangements apply |

Authority code: 7940

| | |
|-------------------|---|
| Category/Program | Section 100 (Efficient funding of chemotherapy) |
| Condition | Multiple Myeloma |
| Prescriber type | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| PBS Indication | Symptomatic multiple myeloma |
| Treatment phase | Continuing PBS-subsidised treatment |
| Restriction | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required – Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria | <p>Patient must have received an initial authority prescription for bortezomib for newly diagnosed symptomatic multiple myeloma and be ineligible for high dose chemotherapy, AND Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition, AND Patient must not have achieved a best confirmed response to bortezomib at the time of prescribing, AND Patient must not be receiving concomitant PBS-subsidised thalidomide or its analogues, AND The treatment must be in combination with a corticosteroid and melphalan or cyclophosphamide, <i>OR</i> <i>The treatment must be in combination with lenalidomide and dexamethasone,</i> AND Patient must not receive more than 5 cycles of treatment with bortezomib under this restriction.</p> <p>Continuing PBS-subsidised supply required that the gap between the initial PBS-subsidised treatment with this drug for this condition and this continuing treatment is no more than 6 months.</p> |
| Note | Special Pricing Arrangements apply |

9 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.

10 Sponsor's Comment

Celgene welcomes the PBAC's recommendation to list lenalidomide in combination with bortezomib and dexamethasone (RVd) for the treatment of patients with NDMM on the PBS. Celgene would like to thank clinicians, patients and advocacy groups for their contribution in helping the PBAC recognise the importance of RVd for patients living with MM in Australia and the PBAC for working proactively to implement a major priority identified at the Multiple Myeloma Stakeholder Meeting held in May 2018.

Celgene are now working with the Department of Health to implement this recommendation and make this important treatment option available to patients newly diagnosed with MM in a timely manner.